ORGANOTHERAPY

IN

GENERAL PRACTICE

"Still more earnestly do I believe that the study of the whole field of the Internal Secretions will enable us to detect and correct morbid tendencies with a degree of success which has been denied to the older methods. The microbe—the seed—has ruled the immediate past; the future is with the soil, the endocrine glands." (Leonard Williams, "Minor Maladies," 4th Edition.)

"Since the development of the bacterial theory of infection, there is probably no pathological concept that has latterly so dominated modern medicine as the doctrine of the internal secretions of the ductless glands." (Fielding H. Garrison, Lieut. Colonel, Medical Corps, U. S. Army: "Endocrinology and Metabolism," Vol. I, 1922.)

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"The endocrines are functionally basic to all principles of physiology; in fact, endocrinology is physiology, and no physician or surgeon can qualify adequately in any phase of medical science who is failing in knowledge of this subject. We must all be endocrinologists to practice successfully the art of healing, which is our paramount function." ("The Interrelation of the Endocrines and the Vegetative Nervous System," William V. Garretson, *New York Medical Journal,* March 15, 1922.)

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PREFACE

"Organotherapy in General Practice" is offered to the medical profession in the hope that it will prove of real service in supplying a condensed, dependable text-book covering the entire field, and be of value to the general practitioner in the diagnosis and treatment of those conditions in which Organotherapy is now the accepted method of treatment.

The books devoted to this subject usually cover only one gland, one section or one phase of the subject—purely physiological aspects or diseases of the endocrine glands themselves. Original research is usually reported in scientific journals of high character but very small circulation, and often does not come to the attention of the general practitioner for a long time.

The growth of this form of therapy has been steady and progressive in all parts of the world, so that today it forms a substantial part of all medical practice, and endocrine preparations of some type are included in the pharmacopœias of the United States, Great Britain, and France. Prof. Arthur Biedl of Vienna, an international authority in endocrinology, has said: "Organo preparations have enriched our medicinal resources to an undreamed of extent, and for the most part with substances that cannot be imitated."

The purpose of this book will have been accomplished if the general practitioner is aided in some degree in using Organotherapy in his everyday practice, for it furnishes an effective means for the treatment, relief and cure of many human ailments which are beyond aid by the older agents of the physician's armamentarium.

G. W. Carnrick Co.

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THERAPEUTIC INDEX

References in heavy face type refer to Treatment.
Those in light face to general discussion.

"Pituitary Obesity. Girl of nineteen; very small hands, small mouth; adiposity confined to lower segments largely; fed on thyroid injudiciously and collapse ensued. Improved very much on pituitary feeding. Has small enclosed sella turcica." (From "Lectures on Endocrinology," by Dr. Walter Timme.)

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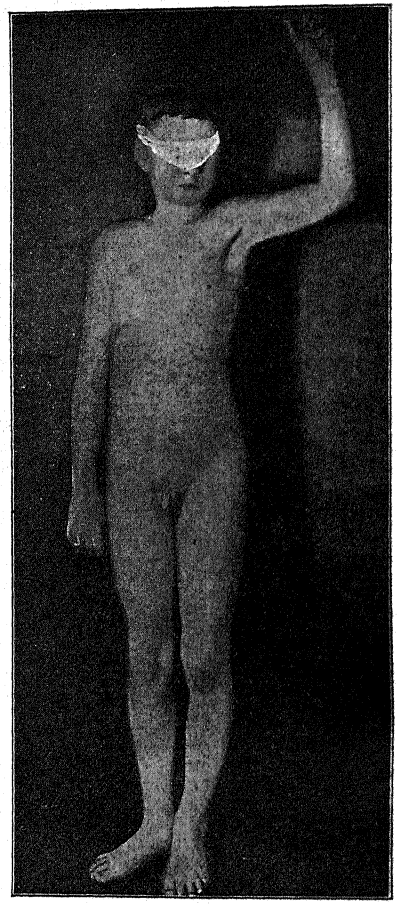
Note particularly the difference in type of distribution of fat from that found in thyroid obesity. In thyroid obesity there is a tendency to uniform distribution of fat all over the body.



"Case of Status Thymicolymphaticus Emerging from this Condition as Described in Text. This case has a very small sella, has an undeveloped genital system with scrotal implantation about the base of the penis; has no hair on body; bruises easily as seen from slight pressure of thumb on raised arm a few minutes before picture was taken; has spasms of muscles and enuresis; x-ray shows thymic shadow; low blood sugar, low carbon dioxide tension. Patient is a pathological liar. Age thirteen years." (From "Lectures on Endocrinology," by Dr. Walter Timme.)

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" Far-Advanced Acromegalic: pigment patches on shoulders and arms antedated the acromegaly. They followed upon an obscure abdominal affection, probably tuberculous; and are an expression of suprarenal insufficiency. The attempt by the pituitary gland to compensate for the deficient suprarenals possibly accounted for the acromegalic symptoms. Sella was markedly enlarged." (From " Lectures on Endocrinology," by Dr. Walter Timme.)
Paul B. Hoeber, Inc., New York, Publishers. By permission of author and publishers.

" Seemingly Exophthalmic Goiter without Goiter. Blood pressure 180 to 150 systolic; pulse 120; marked exophthalmos; deficient hair on body; outer eyebrow lacking; psoriasis; cessation of menses for one year; no loss of weight; all symptomatic of deficient thyroid activity. When fed on thyroid gland, great rise of blood pressure with rapid exhaustion following. This is a case explained in the text as being due to hyperadrenia and not hyperthyroidism." (From " Lectures on Endocrinology," by Dr. Walter Timme.)
Paul B. Hoeber, Inc., New York. Publishers. By permission of author and publishers.

Hypothyroidism. (Partly diagrammatic.) Moderately advanced. Shows thickened, wrinkled skin. Dull expression. Puffy features. Thickened lips.

PART I

GENERAL PRINCIPLES

The widespread interest and intensive study of the internal secretions is of relatively recent date. In a period of thirty-five years the whole structure and point of view of physiology and functional pathology has been revised, and some of the most fundamental concepts of general biology have been reconstructed on the basis of internal secretion effects. The germ idea, however, undeveloped and vaguely formulated, may be found in various periods of medicine from the time of Hippocrates. Egyptian, Greek and Roman medicine all included beliefs and practices which were in their fundamentals related to the modern theory of internal secretions. The Indian Ayurveda of 1800, B. C., contains references to it. Organotherapy, or the application of these principles to the treatment of disease, tended to demand more attention and to precede careful investigation of the purely physiological aspects in antiquity, as well as at the present time. Thus, while the literature up to about 1800 is rich in references to the use of organotherapeutic substances for the treatment of disease, there are very few extensive attempts to formulate any general theories of their mode of action, or of the fundamental action of the internal secretion structures in physiology. Following Hippocrates, Celsus, Pliny, Aristotle, Paracelsus, Galen and many others either described organotherapeutic uses, the internal secretion structures themselves or vague theories of function. The pharmacopoeias of London and the continent contained many substances of animal origin, and of the most diverse kind. Such substances derived from the human body were not uncommon. According to Biedl, there were 152 products of animal origin in the apothecary shops of Innsbruck in 1765.

The Forerunners of Organotherapy

Some older theories of medicine, among them Galen's "humoral" theory, might be considered in some respects to be the forerunners of present-day theory. Galen, without any knowledge of the circulation of the blood and lymph, regarded a faulty mixing or proportion of the four juices (gall, phlegm, blood and pancreatic juice) of the body as the cause of disease. In his work of extending and confirming this theory, Theophile de Bordeu in 1775 was probably the first to clearly formulate a general theory of internal secretions, in many respects very similar to the theory as now understood. Bordeu's work was largely speculative, but in his treatise (1775) he clearly stated that each organ serves as the laboratory of a specific substance which enters the blood, and that these substances are useful to the organism and necessary to maintain its integrity. In the meantime, the earlier crude attempts at organotherapy, which included the administration of filthy substances, excreta of animals, lice, snake skin, vipers, etc., had been discarded and there appear references to a practice which seems to have been a forerunner of modern organotherapy and which,

however vaguely conceived, was predicated upon the same theory as that held today—the substitutive and homostimulative therapy of Hallion. This was the practice of administering the organs of healthy animals for diseases of those same organs in man.

Following Bordeu's pioneer work (which may have been influenced by Diderot, whose "Elements de Physiologie" contained a discussion of the principles of internal secretion), other workers published articles and reports of research which clearly showed that the concept of internal secretion was held in more or less developed form.

Legallois (1801) suggested that blood undergoes change as a result of acquiring substances from the organs through which it passes. A. A. Berthold in 1849 furnished experimental evidence of the production of substances in the internal secreting tissues which exerted profound effects on the animal, by his experiments and observations in grafting and transplanting the testes of cocks. Berthold was perhaps the first to furnish actual experimental data, correctly interpreted, demonstrating the internal secretions, for he showed that, even after severance of all the nerves to the gonads, the sex impulse was not destroyed.

In 1855 Claude Bernard coined the words "internal secretion," as distinguished from external secretion. He regarded glycogen as the internal secretion of the liver and definitely showed the synthetic capacity of the body cells to produce new compounds. In 1856 the first work by M. Schiff of thyroidectomy in animals was performed, and suggested internal secretion effects. These are not the only names that might be mentioned as contributing to the subject between 1800 and 1889, which latter may be regarded as the birth date of both endocrinology and organotherapy, but they are the most important. With full knowledge of all the preceding work and its value, for many reasons the actual beginning of the subject is almost universally considered to be June 1, 1889, the date of the now famous lecture of Charles Edward Brown-Sequard before the Société de Biologie of Paris. Whereas the earlier work of other investigators passed by practically without notice, Brown-Sequard's announcement attracted the widest attention and served to stimulate research and investigation in the subject up to the present time. Brown-Sequard himself had published the results of his researches in this field years before, but this received no more attention than the work of others. In 1889, however, he announced the results of the injection of testicular extracts in his own person. At that time, 72 years of age, he stated that these extracts produced a remarkable increase in physical strength and mental activity. Appetite, intestinal and other bodily functions were all beneficially affected, the sense of physical well-being heightened and his ability for application to intensive work greatly increased. Brown-Sequard was much ridiculed, and even today it is not as generally understood as it should be that these experiments were simply a small part—experimental data—of his very extensive researches on the fundamental character of the internal secretions. His early formulation, which in all respects was the most comprehensive up to that time and today accurately expresses the theory, was stated as follows, in a paper by Brown-Sequard and d'Arsonval in 1891:[1]

The Birth of Modern Organotherapy

> "We admit that each tissue and, more generally, each cell of the organism secretes on its own account certain products or special ferments, which, through this medium, influence all other cells of the body, a definite solidarity being thus established among all the cells through a mechanism other than the nervous system. . . . All the tissues (glands or other organs) have thus a special internal secretion and so give to the blood something more than the waste products of metabolism. The internal secretions, whether by direct favorable influence or whether through the hindrances of deleterious processes, seem to be of great utility in maintaining the organism in its normal state."

According to Biedl, D. Hanseman (1891) had reached an analogous conclusion, although starting from a different point of view; but certainly there has been no general knowledge of such work. In this epochal year also, von Mering and Minkowski made their classical research in artificial diabetes, and practically if not absolutely proved the internal secretory action of the pancreas.

Prior to this real beginning, Thomas Addison in 1855, as a result of clinical and pathological observations, described the disease now known by his name as due to destruction of the suprarenal glands. The clinical, pathological and experimental physiological investigation has increased enormously since 1889, until today no phase of modern medicine or biology receives a greater attention. A review of anything but the more important phases of this development would be impossible here.

Present-Day Conception of Internal Secretions

Today the internal secretions are regarded as a means of maintaining a harmonious interaction between the various cells, tissues, organs and parts of the animal body. While it is conceivable that an internal secretion might be furnished by all tissues and by each cell of the body, it is probable that only those specialized tissues making up the internal secretory organs give rise to substances which in course of organic evolution have become a definite and fixed part of physiology. The organs which are thus classified as giving definite internal secretions are the Pituitary, Thyroid, Parathyroids, Adrenals, Gonads, insular part of the Pancreas and the Duodenum. Those having an internal secretion about which less is known are the Prostate, Spleen, Kidney, Liver, Mammary, Thymus and Pineal. The function of maintaining (in part) this interaction, the "consensus partium," includes all the diverse functions that are known of the internal secretions in particular effects, such as growth promoting, pressor, metabolistic, etc.

This action of the internal secretions is supplementary to that of the nervous system and has been said to antedate it as a primitive coördinating system. Today there is believed to be a close relationship between the nervous system and internal secretion mechanism, particularly the vegetative nervous system (described later). Biedl says: "Formerly all organic correlation was assumed to be nervous; at the present day, even the nervous relation is largely considered to be induced by chemical factors."

TERMINOLOGY

Various terms are used to describe the substances which we have referred to as internal secretions, and the organs producing them. The one now very generally accepted as describing the organs themselves, and appearing in the literature of practically all countries, is "Endocrine" (Greek: Endo—within, and Krino—I separate out). Endocrine is applied to all the tissues and organs giving rise to an internal secretion. It replaces the older term "ductless gland," which was unsatisfactory for the reason that some of the internal secreting organs have both an internal and an external secretion, and hence *do* have ducts. The internal secretions themselves are usually referred to as hormones (Greek: hormao—I arouse), a term coined by Starling. Schäfer has suggested that, inasmuch as this type of action is not always one of stimulation but frequently also one of inhibition, "hormone" is not appropriate for all the internal secretions, and has suggested the word "autocoid" (Greek: autos—self, and akos—a drug). Autocoids are divided into two classes: "hormones," which stimulate or increase, and "chalones" (Greek: chalao—to make slack), which depress activity. This classification has no wide acceptance and is, moreover, not entirely satisfactory as, dependent upon the amount, the tissue and the concentration, the same internal secretion may be both stimulatory and inhibitory. Cryptorrhetic, suggested by Matthews, has been used by a very limited number of authors. A very acceptable term has become current in the German, and has recently appeared in the American literature, "Incretion." It was first used by Abderhalden at the suggestion of Roux, and is intended to apply to all internal secretions, in the same manner as the term "Hormone."

Gley uses the word "Harmozone" to describe those internal secretions which are active in growth during ontogenetic development ("morphogenetic substances"), and "parhormones" to describe substances which result from antitoxic function of the organism. These substances, such as urea, CO_2, etc., might come within a definition of an internal secretion, but they are not regarded as such, and it seems advisable to follow a classification such as Gley's. The vital distinction in the character of endocrine action, mere functional regulation on the one hand, and the profound growth effects described as harmozone effects on the other, should receive general recognition. He describes hormones as substances which provoke functional activity. It has been said by some (Keith, Bolk and others) that the development of racial characteristics is dependent upon the character and extent of the development of the endocrine organs, and that different races may be classified as hypophyseal types, thyroid types, etc. It is known that the pituitary, thyroid, gonads, adrenals, etc., are concerned with particular phases of growth and development, such as height, pigmentation, form, etc., and the subject undoubtedly demands further study.

A definition of what is included in these various terms may now be given. By "internal secretion" and synonymous terms is meant those specific chemical substances which are secreted by special glandular or other tissues and passed into the blood or lymph, and which influence the functional activity, growth or development of other distant organs. These substances, which are specific for each one of the endocrine organs, are not used in the

upbuilding of the cells and their action may be catalytic. Organized substances with a definite morphology are not included. The classification of a structure as an endocrine organ is not dependent upon the presence or absence of epithelial glandular tissue, for, although this is the rule, some structures, such as the posterior lobe of the pituitary and the adrenal medulla, are not glandular or epithelial and yet are considered as giving rise to an internal secretion. While it is open to question as to whether they are the characteristic and sole hormones of the respective glands, thyroxin and epinephrin are the only ones whose chemical structure is known. Insuline, from the Islands of Langerhans of the pancreas, and tethelin, from the anterior pituitary, have been isolated in something approaching pure form, but are chemically unknown.

MECHANISM OF INTERNAL SECRETION EFFECTS

There are a number of possibilities as to the manner in which the internal secretions, active chemical substances, may bring about their characteristic effects, but there are two methods which are generally held to account for the great majority of internal secretion effects—direct action on the cell metabolism itself and through the medium of the vegetative nervous system. Both methods have been demonstrated. Epinephrin (see page 100) produces its characteristic effects by its action on the myoneural junction of the vegetative nerves. This junction is composed of a special receptive substance which has been described by Langley. The effects of epinephrin are, therefore, the effects of stimulation of the sympathetic part of the vegetative nervous system. Pituitary extracts, on the other hand, directly stimulate the smooth muscle itself (see page 117), as is the case with thyroid (see page 48), which directly affects all cell metabolism, although it is also believed to act in sensitizing the myoneural junctions for the action of other internal secretions. The assumed antitoxic or neutralizing function of the endocrine glands would be a function and a mechanism lying outside of the definitions and description here given, but such function may be secondary rather than primary and be contingent upon the direct action exerted upon metabolism. The mechanism of the profound harmozone effects of Gley is unknown.

The first mode of hormone action is that of direct action on cell metabolism. This is known to take place in some instances and may be a factor in many internal secretion actions. The action may be general and affect the metabolism of all cells (thyroid) or specific and affect only certain types of cell (pituitary). Most of the hormones are of the latter type. Cell membranes have a large lipoid content, and the entrance of substances into the cell is dependent upon the permeability of the substance through this lipoid membrane. It has been shown by Overton[3] that specific permeability of cell membranes is in large measure dependent upon the lipoids of the plasma membrane—a thin lipoid film surrounding the cell—and hormone action may be dependent upon its ability to penetrate this membrane. Hormones may, therefore, be selective for certain cells by reason of their permeability for the cell membrane, by their rate of diffusion, etc. That there is a specific cell " receptor " for the hormone on the

tissue of selection is a possibility. This is Ehrlich's explanation in which substances react chemically with the cell, which is acted upon or chosen because it has the reacting group or side chain necessary for chemical combination. In general, however, it is probable that direct hormone action on particular cells—specific action—is dependent upon such physical action as easy solubility in the particular cell membrane, adsorption, etc.

The hormone, while it may or may not form chemical combination in effecting entrance to the cell, probably acts as a catalyst on the cell metabolism after entering the cell body. This, however, is by no means established conclusively. That hormone action is one of catalysis is assumed from the minute quantities necessary to produce their effects. but other types of action are not excluded by this. Robertson says,[18] "Finally, we are not possessed of any evidence which controverts the view that the hormones themselves may exert their actions by entering into the composition of the cells which they affect." The hormones are not enzymes and do not produce their effects by virtue of such properties.

The second mode of hormone action is through the medium of the vegetative nervous system, a method which has been thoroughly demonstrated and which, with the direct action on cell metabolism described above, probably accounts for the great majority of internal secretion effects. (See also page 45 for an electro-chemical theory of mechanism.) The importance of this second mode of action is sufficient to demand a somewhat detailed description of the vegetative nervous system itself and its relation to the internal secretions, and the clinical conditions arising as a result of its disturbed function.

THE VEGETATIVE (AUTONOMIC) NERVOUS SYSTEM

The internal secretions are conceived to be a system for the correlation of the activities of the various parts of the organism: a system which of itself is insufficient to meet the needs of the higher forms of animal life and which with the vegetative and central nervous systems makes possible the remarkably efficient coördinations of the most complex animal organism. The function of the rapid adjustments of the body is almost wholly one of the central nervous system, but in the more slowly effected vegetative functions the vegetative nervous system and the internal secretions constitute the essential mechanism. The action of the two—the vegetative nervous and the endocrine—are so intimately related and their processes so interdependent that it is impossible to consider one without the other, for the tonicity or irritability of the vegetative system is regulated through the endocrine organs.

In the diagnosis and treatment of disease, this relationship is particularly important, for most diseases in which organotherapy has a field may be considered to be imperfect correlations between the several parts of the highly developed and specialized vertebrate organism. The vegetative nervous system and the internal secretions are important both in the etiology and symptomatology of such diseases. In the manifold manifestations of disease—disturbances of glands, altered metabolism, reflected pain, intestinal spasms, cardiac disturbances and the psychic accompaniments, feelings,

moods, etc.—we may investigate the cause and mechanism of the disturbances in these physiological regulators and coördinators. Such investigation of disease, regarded as changing, living, disturbed physiological processes, is quite different from that followed in the period of medicine now passed by, in which disease was interpreted in the terms of dead pictures of pathology and structural end effects, the terminal stages of the active process in life. The relation of the psychic elements in disease to the physical has fuller meaning when the effects of conscious states upon the viscera and perhaps the converse relation are considered. The relation of the emotions—fright, fear, etc.—to the activity of the adrenal system has been described by Cannon and is an example of such a relationship. The following from Higier admirably summarizes this matter:

> "The pathological changes of the secretions of many endocrinous glands—thyroid, pineal, hypophysis, sex glands—cause definite psychic manifestations (as for instance in Graves' disease, myxedema, acromegaly, castration) which lie essentially in the realm of affective life. A series of physiological conditions, among which puberty, pregnancy, menstruation, and old age may be mentioned, are frequently accompanied by a modification of the affective process, and, at the same time, by an alteration of the normal secretions of some glands (sex glands and thyroid gland). Definite diseases which are intimately related to the condition of increased or decreased secretion of endocrinous glands not infrequently follow directly upon violent emotions. The objective signs of some emotional excitements (palpitation of the heart, sweating, mydriasis) are equivalent to a complex of symptoms as we see them shown in dysglandulism, as for example in Graves' disease, Addison's disease and eunuchoidism.
>
> "However we may think of the significance of the glands of internal secretion as etiological agents, the fact still remains that, on the basis of clinical observations, the influence of many of the products of internal secretions upon the manifestations of the affective life are undeniably established. But now a new difficulty arises: to appreciate as a real fact the causal relation between internal secretions and cortical activity. Even though today the old theory of the sympathetic is placed in the background in favor of other hypotheses, yet the fact of the close relationship between the glands of internal secretion and the sympathetic remains unchanged."

The following brief description of the vegetative nervous system, the system made up of all the motor efferent nerves which supply the involuntary organs, and in control of the vegetative processes of the body which are almost wholly independent of consciousness, is given as being essential to a general understanding of the disturbed physiological processes associated with faulty function of the internal secretory organs. The nomenclature descriptive of the vegetative nervous system varies. It is sometimes referred to as the autonomic (Langley), the vegetative (Meyer) and the involuntary (Gaskell). Using Langley's nomenclature, the autonomic nervous system is divided into two general divisions: the sympathetic and the parasympathetic.

The Sympathetic System

The *sympathetic* or thoracico-lumbar portion comprises a chain of ganglia lying on each side of the vertebral column, in the thoracic region, one ganglion for each vertebra, and extending from the first thoracic to the fourth or fifth lumbar vertebra. In the cervical region on each side the uniform segmental arrangement is not typical and consists of three ganglia, the superior, middle and inferior. From the sympathetic ganglia fibers pass by way of the spinal nerves and the blood vessels for distribution to the skin, blood vessels, glands and abdominal and pelvic viscera. This portion most nearly represents the primitive segmental arrangement of lower forms. From this portion vasomotor, sweat, and pilomotor fibers pass to the surface of the body and to the viscera. The chromaffin system, of which the suprarenal medulla is the largest single unit, is usually included as a part of the sympathetic system. Embryologically the two develop from the same germinal layer and masses of the chromaffin cells are found in the sympathetic ganglia (paraganglia). The relationship in functional activity is well known—the internal secretion of the chromaffin tissue, epinephrin, is the great excitant of sympathetic activity, so that the interactions between the two are remarkably close. Epinephrin excites only those tissues innervated by the sympathetic and its effect is always one of furthering the normal activity. The activation may be either one of stimulation or inhibition.

The general effects of sympathetic activity are for the preparation of the body for quick violent reaction to its environment. In this it prepares for the action of the skeletal muscles under voluntary control, and consists of acceleration of the heart, increased blood supply to the muscles and diminution of blood supply to the periphery (constriction of peripheral arterioles and those of the splanchnic area) dilatation of pupil, inhibition of activity of the gastrointestinal tract with diminution of its blood supply, erection of the hair and secretion of the sweat glands. Such a picture is presented in those states described by Cannon—fear, pain, rage—and the diffuse effects of the sympathetic are clearly in evidence. In these effects, then, the sympathetic prepares the animal for its offensive and defensive reactions.

The Parasympathetic System

The *parasympathetic* includes the fibers lying, for the most part, in the vagus (the *bulbar* portion) and also, in lesser extent, in the third, seventh, ninth and eleventh cranial nerves, and the *sacral* portion consisting of fibers leaving the cord in the nerve trunks of the second, third, and fourth spinal sacral nerves. Also, here should be included the small midbrain part (tectal) which passes through the oculomotor nerve, through the ciliary ganglion, into the ciliary muscle of the eye. From the bulbar part by fibers passing through the seventh and ninth nerves, the salivary glands are supplied. Through the vagus, by far the most important part of the parasympathetic, are supplied fibers to the heart, bronchi, esophagus, stomach, intestine and pancreas. From the sacral portion through the nervus erigens are supplied the descending colon, rectum, anus and genital organs.

That part of the vegetative system in the intestine described as the plexuses of Auerbach and Meissner is not clearly related to either of the two great divisions and at the present time is placed in a class of its own.

The effects of parasympathetic action are to slow the action of the heart, increase the function of the digestive tract, stimulate salivary and digestive juice excretion and aid in the general upbuilding and anabolic activity of the body. The general effect, therefore, is of conserving bodily resources, building up a reserve of energy and energy-yielding material to be called upon and used in time of need by the action of the sympathetic.

The Mechanism in Vegetative Neurology

The normal actions of the autonomic system are reflexes taking place over an unusual type of reflex arc. The afferent paths are not understood as clearly as the efferent, and the autonomic nervous system is frequently described as an efferent or motor system only. Many complete arcs—that is, complete centrifugal and centripetal paths—have been demonstrated, however. Afferent visceral fibers are found in the ninth and tenth cranial nerves, extending from the viscera through the same course as those of the efferent fibers. The afferent fibers of the vagus are of this kind. An example illustrating a complete arc in which both afferent and efferent pathways are known is given by Higier in the ejaculation reflex:

> "The stimulation aroused in the sensory end organ, the glans penis, travels via the nervus dorsalis penis and the nervus pudendus communis to a spinal ganglion of the lower sacral roots and from here via fibers of the cauda equina to the lumbar ejaculation center, where the centripetal part of the arc ends. From this point, the motor activity passes by the lumbar communicating branches and the hypogastric nerves to the pelvic tracts and from here via the gray post-cellular fibers to the powerful smooth musculature of the end organs, the spermatic cord, seminal vesicles and prostate."

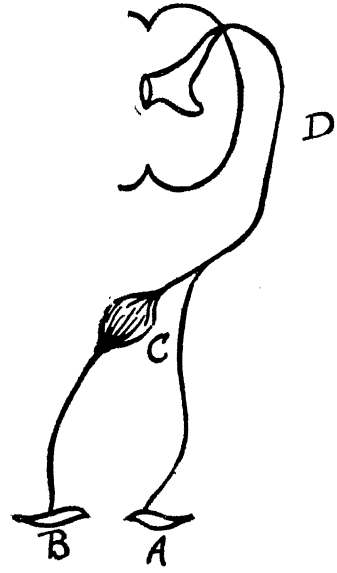
For most of the purely vegetative reflexes, however, and those in which there is no question of impulses arising from the surface of the body and aiding in the adaptive mechanism of the organism to its environment, a much shorter and simpler arc is presumed. In all these reflexes in which the sensory impulses do not reach consciousness (the stomach, intestines, heart, and other viscera) there is the so-called "axon reflex," in which the reflex lies in a vegetative ganglion contained in or near the organ itself and not in the spinal cord. The axon reflex is based upon the concept that a preganglionic fiber may form a connection (synapse) with several postganglionic fibers, so that stimulation at *A* in Schema No. 1 may set up an action in *B*. A branch fiber of *A* perhaps passes down to *B*, so that stimulation of *A* sends an impulse to *B*, as well as to the cord.

No evidence is at hand to show that the reflex takes place in either the lateral or pelvic abdominal ganglia. Such an arc made up of afferent pathways connecting with efferent fibers is not known.

The axon reflex offers a mechanism not involving nervous structures in the cord or centers far removed from the organ involved, and is a possible explanation of the widely quoted experiments of Goltz and Ewald, who maintained dogs in fair condition for long periods after removal of the

cord below the cervical region. In one case such complex actions as birth of a litter and suckling the young were noted.

The complex reflex arc with centripetal paths to the cord and thence to the higher centers and centrifugal paths back to the organ are present in those reactions which involve the reaction of the organism to its outer environment. Here there is the stimulation of sensory pathways; the interposition of pathways in the central nervous system itself; the outflowing impulses over the efferent vegetative pathways. This type of action emphasizes the fact that, although the function of many of the organs



SCHEMA No. 1.

innervated by the vegetative nervous system is in large degree autonomous, there is still a dependence upon and a close relationship with the central nervous system.

Voluntary Control of Vegetative Functions

The afferent side of an arc of this kind may arise from either the surfaces of the body or from the viscera, but the pathway through the central nervous system does not lead to the cerebral cortex but to lower parts of the brain (midbrain). As voluntary motor impulses arise from definite motor areas in the cortex, there is no mechanism for the initiation of motor impulses over them and the autonomic actions are almost wholly removed from voluntary control. Some impulses, however, undoubtedly do reach consciousness over these visceral afferent pathways and give rise to sensations of visceral disease and pain (?), so that neurotic or neuropathic individuals may be aware of such sensations, which furnish a real basis for the sensations and fears of the hypochondriac.

The relations of the central nervous system to the vegetative are, however, not clearly worked out. The centripetal pathways referred to as playing a part in some types of the vegetative reflex arc are considered to be sensory and not vegetative fibers. The relationship of the two, however, is of great interest to the clinician, for it aids in the interpretation of disease symptoms, particularly in visceral reflected pain. Higier says:

> "Some investigators, as Mackenzie and Head, assume the existence of centripetal fibers from organs to spinal cord. On this basis, a middle position between no sensation at all and a specific sensation is taken. This school believes that the fibers from organs to spinal cord do not pass directly to the cortex, but that they first go to the spinal cord and from there the sensation may be relayed to the cortex. This theory has become extremely popular. It accounts for reflex pains occurring in visceral disease, pains which are often not felt in the organs themselves, or not only in them but are also very definitely localized in some skin area. This area corresponds to the spinal cord segment which receives the nerve fibers from the organ involved. There is no doubt of the existence of these hyperalgesic areas of Head, the only doubtful element being the explanation of the entire mechanism of their occurrence. They were described by others before Head, Bassereau (1847), Beau (1866) and Lange. The English authors believed the occurrence of these hyperalgesic areas to be due to the passage of abnormally strong stimuli from the organs to the spinal cord, thus making the sensory fibers there much more sensitive. From this, the corresponding skin areas became oversensitive or hyperalgesic.
>
> "The conclusion from these last mentioned facts is as follows: There are fibers passing from internal organs via the posterior ganglia to the spinal cord which do not give any definite sensation but are sensory in nature and are not to be confused with any vegetative fibers passing to the organs. These fibers are activated by abnormally strong stimuli. It is noteworthy that the Head zones are never as sensitive when the pain stimulus comes merely from the spinal cord fibers as when they come from some stimulation of the cerebrospinal axis impulses from vegetative organs."

Description of a Unit of the Vegetative System

The anatomical arrangement of the autonomic system is quite different from that of the central nerve axis and a unit from the middorsal region, which is typical, is as follows: The sympathetic prevertebral ganglia are joined to each other by communicating fibers to form the sympathetic chain. These ganglia are again joined to the spinal cord by the efferent fibers. The efferent pathways consist of two cells or neurons; the first lies in the lateral horn of gray matter in the cord and its axis cylinder is the "preganglionic fiber." This fiber is medullated and leaves the cord by the anterior root and, as the "white ramus," enters a ganglion of the sympathetic chain. Typically, it ends here in a connection (not anatomically continuous) with the axon of the second

neuron and the pathway is continued to the end organ in the smooth muscle. This junction of the two axons is the "synapse" and the second axon leaving the ganglion and passing back to the spinal nerve trunk to continue its way to the end organ is non-medullated and is the "gray ramus." Actually, the preganglionic fiber may pass through several ganglia before terminating in the synapse. The demonstration of the exact ganglion in which the synapse of a given fiber occurs may be demonstrated pharmacologically by the nicotine method.

In the sympathetic system the preganglionic fibers which are distributed to the surface of the body terminate in the synapse of the sympathetic ganglion and are continued as the gray rami back to the same spinal nerve and follow the course and distribution of that nerve. The fibers to the internal vegetative viscera, blood vessels and glands are distributed in a somewhat different manner. There, preganglionic fibers pass without interruption through the sympathetic chain to outlying ganglia (in the upper portion to the superior cervical ganglion and in the lower portion to the celiac and inferior mesenteric ganglion) and terminate in a synapse. From this ganglion the postganglionic fiber is continued to its end organ. These various ganglia, far removed from the main sympathetic chain, therefore constitute an important part of the sympathetic system.

The nature of this distribution of the sympathetic fibers permits of a very diffuse stimulation. The sympathetic action is not closely localized but diffused over wide areas. This action is apparent in the experiment of Langley, quoted by Langdon Brown:

> "On stimulating a single gray ramus, the hairs will only erect over a single segmental area, but on stimulating a white ramus, erection occurs over a number of areas, usually five or six."

In the parasympathetic the course of the fibers varies greatly from that described as typical for the middorsal region. The preganglionic fibers of the third nerve end in a synapse in the ciliary ganglion. The fibers leaving with the seventh and ninth nerves terminate in the spheno-palatine, otic, sublingual, submaxillary and other sympathetic ganglia, and are distributed to the mucous membrane of the mouth and the salivary glands. The great mass of fibers passing out with the vagus (tenth nerve) pass as preganglionic fibers to the sympathetic ganglia near the viscera, and thence as postganglionic to the end organs in the esophagus, stomach, intestine, part of colon, bronchi, heart and pancreas. From the sacral portion the preganglionic fibers pass as a combined bundle (nervus erigens) to the pelvic plexus. From here the postganglionic fibers supply the external genital organs, rectum, anus and lower colon.

As the parasympathetic fibers have no such arrangement of long postganglionic fibers continued from synapses close to the cord, but have in most instances their synapse in a ganglion close to the innervated organ, their effects are more distinctly localized.

Dual Innervation of Vegetative Structures

Another point of difference from the sensori-motor system is in the character of the fibers of both the sympathetic and parasympathetic systems and the character of the end organs. In the sympathetic and parasympathetic there are both stimulatory and inhibitory fibers and as the vegetative end organ in practically all structures (sweat glands

and erectores pilorum are exclusively sympathetic) receives fibers from both, a vegetative organ typically and completely innervated is finely and delicately balanced in its functions by:

1. Sympathetic stimulatory fibers.
2. Sympathetic inhibitory fibers.
3. Parasympathetic stimulatory fibers.
4. Parasympathetic inhibitory fibers.

Such complete, balanced action of four sets of fibers is not worked out for many tissues and it is probable that in most instances the activities of the sympathetic and parasympathetic are of one kind and opposed to each other.

Between the sympathetic and parasympathetic there is in general a definite physiological antagonism, so that the predominance of the one or the other determines the functional activity of the vegetative organ. Thus, the *sympathetic*

dilates the pupil,
accelerates the action of the heart,
inhibits peristalsis, and the secretions of the salivary juices,
dilates the sphincter ani and bladder;

while the *parasympathetic*

contracts the pupil,
inhibits the heart action,
contracts the intestines,
aids in the passage of the intestinal contents,
stimulates intestinal glandular activity and the secretion of the pancreas and salivary glands,
causes contractions of the bladder.

This balanced action of the two parts of the vegetative system, intimately bound up with the internal secretions which effect all degrees of variation in equilibrium, is of the greatest interest to the endocrinologist who must interpret clinically the symptoms resulting from such variation. The extensive and frequently acute physiological changes of the menopause are one example of a syndrome that is intelligible only through endocrine interpretation. In the numerous clinical conditions encountered in the daily practice of medicine, disturbances of balance of the entire opposed sympathetic and parasympathetic systems are perhaps never encountered, but the dominance of the one or the other in particular sites and in particular tissues is characteristic of a host of everyday ills. This is easily understood when it is remembered that there are almost no known substances which exert an action upon the whole of either system. Practically all the substances used in pharmacology and probably the hormones as well give rise to selective action and local reactions result.

Vagotonia and Sympathicotonia

Clinically two distinct types have been described (Eppinger and Hess), based on this antagonism of the two systems and endocrinological literature contains many references to it. These are vagotonia, in which the parasym-

pathetic predominates, and sympathicotonia, in which the sympathetic exerts the dominant action. These types, as has been previously stated, have been established through the medium of pharmacological investigations. Certain chemical compounds exhibiting a selective action have been used in the artificial stimulation of the one or the other and these resulting physiological states have been taken as types at least of clinical pictures. Adrenalin is the best known example of a sympathetic excitant and pilocarpine and eserine are parasympathetic excitants. Atropine, as is well known, from its action on the vagus, depresses the parasympathetic.

Vagotonia Vagotonia is a clinical condition characterized by contracted pupils not easily dilated by atropine, wide palpebral fissure, salivation, and lacrymation (through corda tympani and lacrymal nerve), tendency to diarrhea and sweating or to colic and constipation, depending upon the extent of the stimulation, increase of secretion and motility of the intestine, strong slow pulsation of the heart and irregular pulse, low blood pressure, irregularities of respiration, eosinophilia, hyperacidity, irregularity and occasional spasm of the esophagus, pylorus, gall bladder and colon, cold extremities, bronchial spasm and tendency to incontinence of urine and feces. Marked improvement of the symptoms follows the administration of atropine, particularly those referable to the gastrointestinal tract. Pilocarpine aggravates the symptoms and a hypodermatic injection may serve to establish a diagnosis. Higier states that atropine and adrenalin affect the symptoms of vagotonia favorably and pilocarpine unfavorably. For such diagnostic procedures he states the hypodermic dosage to be as follows: atropine 1 mg. (gr. 1/70), pilocarpine 1 cg. (gr. 1/7), adrenalin 1 c. c. (m. 15). Vagotonia is much more common in the young or at least in those of middle age than in those of more advanced years. (Caution with such dose of atropine.)

Sympathicotonia The antitype to the above condition, sympathicotonia, is characterized by a tendency to tachycardia, large pupils, scanty lacrymation, lessened secretion of the mucosa of the nasopharynx and of the gastrointestinal tract, hypochlorhydria, relaxation of the muscles of the intestine, increased pulse rate and blood pressure, retardation of the passage of food from stomach to intestines.

ORGANOTHERAPY

As has been noted, organotherapy is a very ancient system of treatment. At first, perhaps imposed by religious and other motives, it gradually acquired some scientific basis, so that at the time of Brown-Sequard's experiments it was not wholly irrational. The formulation of the internal secretion theory and the development of the purely physiological investigations gave it a firm basis, which is expressed by Biedl[1] as follows:

> "It starts with the premise that the internal secretion of an organ is contained in the tissues, or the juices they secrete. Even if the total of active substances present in the organs is not considerable, yet where there is a high degree of activity of the substances, the desired compensatory effect may be attained, especially when the medication is administered for a long time. The brilliant

results of organotherapy in disease conditions, due to lack of the thyroid gland, confirm the correctness of this assumption. Similar, although by no means as dazzling, results have been obtained with other organs, so that we may well say that organo preparations have enriched our medicinal resources to an undreamed of extent, and for the most part with substances that can not be imitated."

The rational physiological basis of organotherapy has been referred to. The enormous influence of the internal secretions in general physiology and in the profound processes of physical and mental growth and development will be described under the individual glands. The administration of these substances in therapeutics enables us to influence and change physiological function and thus modify the course of disease processes. It has been suggested that this is the normal physiological way in which to treat disease, for it is the way in which the body itself effects necessary changes. The mechanism of organotherapy, some knowledge of which is a prerequisite to rational application, may be as follows:

1. Substitutive

In substitutive organotherapy there is an introduction into the organism of the specific substances formed by the gland in normal physiology—the administered product substitutes for lessened or faulty secretion of the affected gland. J. T. Halsey in "Endocrinology and Metabolism" says:[5] "At first it was believed that such glandular preparations could act only substitutionally, that is, that the substances administered acted in place of the absent or diminished secretion of the patient's gland, but very soon it became apparent that all the results obtained could not be explained so simply, and that there must be other modes of action." These other ways will now be discussed. Some doubt has been thrown on the question of a pure substitution therapy, and it has been held that the effects are always produced through the mediation of the organ in the animal. While this may in most instances be true, there are undoubtedly some instances of purely substitution effects—effects which are produced immediately and directly. Insuline effects in diabetes are of this kind, as well as ovarian therapy for the abnormal conditions following the menopause.

2. Homostimulation

The homostimulative properties of organotherapeutic substances are, in all respects, the most valuable of their actions. The postulate was originally that of Hallion, and it is usually referred to as "Hallion's Law." "The extract of an organ administered in suitable amount has an elective stimulating action on the functional activity of the same organ in the patient to whom it is administered." This principle has been subjected to much investigation and its validity questioned, but at the present time is generally accepted. Even physiologists who have examined the facts most critically recognize the basic truth of this principle. Hoskins says:[6] "There is some definite evidence in its support, but the extent of its applicability remains for future determination."

Reference has been made to the belief held by some that organotherapy is effective *only* through its action in stimulating the homologous organ This is supported by the generally ineffective use of gland extracts in relieving symptoms of total ablation as opposed to the successful results in the states of partial insufficiency. Biedl says:[7]

> "On the whole, practical experience has confirmed the deductions drawn from theoretical considerations that organotherapy produces the best results in cases in which there is a partial defect of the endocrine function in one direction or the other; also in cases of what the French term 'petite insuffisance.' Here, where there is a slight lack of hormones, a satisfactory therapeutic action can, for the most part, be obtained. This may be due, not to the quantitative compensation of the lacking hormone, but possibly also to the fact that the partially insufficient hormone organ itself is stimulated to increased function."

This method of mediation through the like organ in the body may explain the well-known fact that a "physiological deficit" forms the best basis for effective organotherapeutic action. The homostimulative effects have been demonstrated in a variety of ways and in numerous endocrine organs. The following refer to the thyroid:

> "Thyroid extract contains a variety of specific substances. These are, independent of the colloidal material, the substances which only the thyroid can manufacture and which it utilizes to build up its own protoplasm or manufacture its secretions. When these substances are introduced into the circulation, it seems as if the thyroid recognizes them; it takes hold of and utilizes them—since they are received already made up—either to repair its own structures or to help it to functionate." (Hallion, La Practique de l'Opotherapie.)[8]
>
> "Thyroid therapy exerts a so unmistakably favorable effect on goiters (other than those of hyperthyroidism) that it has been extensively used both for therapeutic purposes and, especially during an earlier period, as a method of testing the activity of different thyroid preparations. To Reinhold belongs the credit of this discovery, which was promptly confirmed by others, notably by von Bruns. The demonstration that thyroid therapy produces such results is of peculiar interest, and is of great significance for the theory of thyroid therapy in particular and of organotherapy in general, for it furnishes the proof that ingested thyroid substance can exert a curative influence on a diseased thyroid." (Halsey.)[9]

Osborne says:[10]

> "When the thyroid secretion is not entirely absent in a child, thyroid treatment for a time may stimulate the gland to increased activity, and the dose of thyroid extract may then be much diminished."

Feeding, injection and grafting experiments have also demonstrated the selective action of these gland substances for the same organ in the animal. Bell[11] found marked changes in the anterior pituitary following

administration of this substance. "With regard to the experiments carried out with the extract of the anterior lobe, the only definite changes noted were in connection with the anterior lobe of the pituitary, which strangely enough showed evidence, in all cases, of abnormal secretory activity." Similar results were obtained by Rénon and Delille, and other observers have reported the same for other organs (Caussade of suprarenal; Iscovesco of gonads).

Hoskins says:[12]

> "In some instances the effects of administering endocrine gland substances by grafting or otherwise seem to be due, in part at least, to the stimulation of latent cells of the corresponding organs. For example, a case has been described by Morris (1916) in which a testicular graft was implanted to compensate for atrophy of the gonads. The procedure resulted in marked development of the atrophic testes which had been left in situ."

There appear to be two related processes in the mechanism of "homostimulation." This distinction is contained in the above quotation from Hallion relative to the thyroid. There is first a *stimulation* to increased functional activity of the homologous organ and, secondly, there is an *actual rebuilding* of the affected organ. The first of these actions has an analogue in the circulation of the bile. Bile salts are reabsorbed from the intestine and are again taken up by the liver (and only by the liver) and are the most effective cholagogue known. In like manner the hormones selectively stimulate the organs which produce them.

The action of organotherapeutic extracts, in aiding in the *restoration* of an injured organ, is readily explicable and is well stated by Hallion:[13] "It seems as if opotherapy, by supplying to a diseased organ the structural material from which the organ is made, may give the organ a chance to recuperate without too much output of energy." While it is entirely possible that mere substitutive action, in relieving an overfunctioning and partially damaged organ from some of its work, might permit the restoration and regeneration of the organ, it seems more probable that in offering the particular amino acids, proteins and complexes which are necessary for the building of particular tissues the organs are spared the synthetic effort required in the case of utilizing unlike proteins. This is an established principle of general physiology, the following statement of which is taken from MacLeod:[14]

> "* * * The protein molecule is broken down into its ultimate building stones, the amino acids, by the digestive enzymes of the gastrointestinal tract. These amino acids are absorbed into the blood, by which they are carried to the various organs and tissues, which sift out the amino acids and use those of them which they require for the reconstruction of their broken-down protein. The amino acids not required for the process, along with those which may be liberated in the tissues themselves by disintegration of tissue proteins, are then split into two portions, one represented by ammonia and the other by the remainder of the amino acid molecule. The former is excreted as urea and the latter is oxidized to produce energy."

This selective building process, as applied to amino acids and more complex proteins of the administered organotherapeutic substances, certainly does not apply to toxic substances or to many, perhaps all, of the hormones which may be introduced into the organism. The cells do not take up thyroxin in the quantity needed and reject an excess. Thyroid intoxication is a well-known fact. The same may be said of epinephrin, insulin, etc.

3. Symptomatic

In this type advantage is taken of well-known physiological and pharmacological actions of endocrine substances. In the case of some (adrenalin, pituitrin, etc.) this is well known and the substances are employed for the attainment of specific pharmacological actions in the same manner that drugs and other chemical compounds are used. There is no idea, in this form, of effecting any of the profound endocrine (harmozone) actions—the effects are merely pharmacological—constricting blood vessels, raising tone of smooth muscle, etc. There is, moreover, no thought of correcting an underlying endocrine cause. Epinephrin may be used to stimulate heart action and cause vasoconstriction in shock, etc., although lack of epinephrin in the blood is certainly not the cause of the condition.

4. Empirical

Empirical organotherapy is based solely upon the knowledge that the administration of certain gland substances or combinations exercises a favorable action upon a clinical syndrome. Such uses may be without explanation by our limited knowledge, or may even be in discord with some of our most firmly established theories. These uses arose in actual clinical experience, and the sole factor in establishing them has been that they are successful. Many conditions of unknown etiology and pathology, which may or may not be endocrine in origin, respond to treatment by organotherapy.

5. Hormone Therapy by Reciprocal Action (Borchardt)[15]

This is based upon the correlation of the endocrines and includes such measures as the treatment of amenorrhea by pituitary and thyroid. Here, therapy is directed not toward the gland which plays the most important part in the clinical picture, but to another gland in the same chain which acts as an intermediate factor in bringing about the effect, or produces physiological effects which compensate for those of the affected organ. The antagonistic effects of different members of the gland groups also fall in this class.

6. Protein Therapy Effects

Borchardt and others have suggested that some of the effects noted in organotherapy may be due to the therapeutic action of the protein bodies. Certain physiological reactions produced by organotherapy seem almost certainly to be of this type which may be rather common in cases of parenteral introduction of the gland substances. Many extracts, such as pituitary and adrenal, increase the immune reactions. These effects are general

and not limited to particular organs or tissues, and are due to a general protoplasmic activation. Biedl limits "protein therapy effects" to those produced by parenteral administration: "I consider it important to apply this term to a certain concept, that is, the activation of protoplasm or increase of function through the parenteral administration of protein substances and their broken down products. If in some cases, under organotherapy, an ergotropic action cannot unhesitatingly be excluded, yet the chief differences in the hormonic action must first be insisted upon."

GENERAL CHARACTER OF ORGANOTHERAPEUTIC PRODUCTS AND METHOD OF ADMINISTRATION

Desiccated endocrine gland substance is generally used in medicine. This is preferable to extracts of the glands, as solvents may remove active hormones whose chemical composition is unknown, and the protein and elements other than actual hormones are of the highest importance for reasons discussed under Homostimulative Organotherapy. Even extraction of fat, for the sake of a fine pharmaceutical product, is not unattended by danger. Numerous instances are recorded of failure to observe therapeutic effect, due to the fact that the product used had been "degreased" by a process which removed all the active principle. Many products are inert as a result of treatment at too high temperature, so that it is probable that many of the conflicting results appearing in the literature are directly attributable to the use of gland substances which are inert as a result of improper methods of manufacture. Biedl says:

> "The subsequent preparation of the substances (method of desiccation, temperature, pressure, combinations, defatting and de-albuminizing processes, method of conservation, etc.) is of decisive importance, both as regards quantity and very often quality in the effects produced. Under these circumstances, we are able to explain many of the contradictory findings in regard to the action of hormone extracts." [16]

There is almost no class of products in which the physician must rely so wholly upon the integrity and reputation of the manufacturer. The products of G. W. Carnrick Co. are prepared from fresh glands of healthy food animals in our own laboratory and by our own chemists. Every manufacturing process has been carefully tested and every product for which there is a recognized chemical or biological assay is analyzed and standardized. For those products in which an active principle susceptible of assay has not been discovered, our chemists have established certain standards based upon analytical determinations and to which every lot of glands must conform.

Are Organotherapeutic Products Destroyed in the Stomach or Intestine?

There has been much discussion as to whether these substances are destroyed, modified or lose their identity as a result of the action of the digestive enzymes. It may be stated in general that they are not.

"We have already said that the digestive juices do not destroy the extracts, and they still keep their properties. Perhaps hypodermic administration would give more rapid results, but organotherapy has never been a treatment

which was very urgent. It is also possible that the subcutaneous administration would cause the formation of antigen, which possibly might cause the appearance of anaphylactic phenomena."[17] The hormones as chemical compounds probably pass through unaffected by enzyme action, although it is known that they may undergo chemical changes, such as oxidation: epinephrin is well known to be easily oxidized. Others, however, are more stable and pass through unaffected (thyroxin). In the case of those substances in which the hormone is of unknown chemical constitution, such as anterior pituitary, it seems clear that they also must pass from the gastro-intestinal tract into the organism and retain their characteristic effects, for the results of feeding experiments on growth process, etc., by workers in the experimental field show without any question that these substances must pass into the organism from the digestive tract, as is evident from the marked, measurable effects on growth: "The results obtained with pituitary (anterior lobe) tissue which have been cited tend to indicate that the active material in this instance is not totally destroyed by digestive juices, nor totally unassimilable from the digestive tract, but either of these factors nevertheless may have contributed to *reduce* the effect of the administration."[18] We must distinguish here also between the hormone and the protein content of these substances. While some of the hormones may in part undergo change, the protein is simply split into amino acid complexes, which as we have seen are capable of exerting a specific effect on the homologous organ. Of the hormones themselves Hoskins says:[19] "The hormones, on the other hand, are, so far as known, much simpler bodies. They are crystallizable and dialyze freely. They withstand boiling and, according to Abderhalden, are not destroyed by the action of the digestive juices." For those cases in which it is believed that there is some destructive effect in the stomach or intestines sub-lingual absorption may be resorted to.

INTERRELATIONSHIP OF THE ENDOCRINES

The application of the principles of pure physiological endocrinology to organotherapy has been attended by more than the usual difficulties of transition from a pure to an applied science. This has been due largely to the fact that the purely physiological investigations have not been sufficiently developed and elaborated to formulate a sound basis of knowledge and establish a comprehensive theory of internal secretion as a whole. Organotherapy, therefore, has developed not by the extension of the pure science to its application, but, empirically, largely by the method of trial and error. In the meantime, the steady accretions to our fundamental knowledge of the subject make it possible to give rational explanation to our hitherto empirical methods.

Standing as a serious obstacle to the furtherance of rational organotherapy is our profound ignorance of the interrelations of the endocrines and their integrated actions affecting the organism as a whole. While the concept of the interrelationship has very wide currency and may now be stated as an indubitable fact, our knowledge is limited to the particular relationships of the various glands and to their relations with reference to particular functions. Thus, it is very common to speak of the concert of

action among the pituitary, the thyroid, the adrenal cortex and the gonads in growth and development, entirely ignoring the fact that this concert of action may be non-existent in numberless other functions, or that there may be definite antagonism between them. The basis upon which compensatory or synergistic action among particular glands has been predicated is, moreover, often open to serious criticism. Blair Bell (The Pituitary) points to the possibility of error in many of the assumptions currently held. "Thus, because we find an enlargement and apparently an increased activity in the pars anterior and pars posterior of the pituitary after removal of the thyroid, are we to suppose, as has been done by Rogowitsch, Cyon and others, that the function of these parts of the pituitary is supplementary to that of the thyroid? If so, what are we to think of the effect of ovarian removal which produces very similar changes in the pituitary body? Does the secretion of the pituitary also supplement that of the genital glands? It is usually accepted that these things are so, but there is another side of the question. Can this pituitary activity subsequent to castration and thyroidectomy be an expression of an increased activity due to the removal of a restraining influence?"

The mechanism of endocrine interrelationship may, moreover, be indirect. The changes in structure and function which follow injury of one gland may be mediated through the influence of resulting general metabolic change. Such changes in metabolism, caused solely by defect of a single gland, may then cause changes in other endocrine glands which thus react secondarily and contribute their share to the picture of disturbed physiology. This is expressed by Herring[20] as follows:

> "The theory that one endocrine gland exercises a specific influence upon another only touches a part of the question. The changes in metabolism which occur when any gland is disturbed in function must have a widely-spread effect. Many of the metabolic changes undoubtedly take place in the liver, and it is unreasonable to suppose that this organ takes no active part in the problems presented by the ductless glands. Hyperthyroidism provokes such gross changes in the organs of the albino rat that one is drawn to look for the explanation of its effects in the products of a disordered metabolism. Noel Paton has emphasized the importance of the endocrine organs as regulators of metabolism. The investigation of the substances normally formed in the body, and the influence which the ductless glands have upon them, provides a line of research which may eventually lead to the establishment of the endocrine glands as important factors in the regulation of the general metabolism of the body."

Imperfect as it is, however, we must start here in the development of rational organotherapy—in itself a small matter—in relation to the vastly enlarged understanding of physiology in general incident to a better knowledge of endocrine interrelations.

Of perhaps equal importance in removing organotherapy from empiricism is a further extension of our knowledge of the mechanism by which in normal physiology hormone action takes place. In the case of many

hormones of unknown chemical constitution exerting a profound influence on the psychic and somatic functions—hormones of the interrenal system, anterior pituitary, interstitial cells, etc.—the manner in which their effects are produced is a matter of speculation only. In the case of others—thyroxin, adrenalin, etc.—a well-defined action through the vegetative nervous system has been established. This latter constitutes one of the best-known and therefore important parts of our knowledge of the internal secretions, and its application to clinical medicine through the definition of the types sympathicotonia and vagotonia (Eppinger and Hess) makes it one of practical importance as well. It is to be remembered, however, that there are limitations to this application of our knowledge to medicine, for sympathicotonia and vagotonia have been developed largely by pharmacological methods and cannot be used without reservation for the interpretation of actual clinical syndromes. The normal physiological states probably do not in all respects conform to the types that we have established and the existence of such types clinically in any degree resembling the pure type has been seriously questioned. As a basis for the interpretation of various phases of some endocrine syndromes, however, they are useful.

General Endocrine Relations

With the limitations imposed by the state of our knowledge referred to above, it is of practical value to consider the grouping of the endocrines in general classes and, briefly, the relations between the individual glands themselves. With reference to the general effects upon metabolism, growth and development, there has arisen a classification of the glands into two general opposed groups. The classification of Falta (below) appears to be as satisfactory as any of this kind.

1. Acceleratory (catabolic-dissimilatory):
   - (a) Thyroid.
   - (b) Hypophysis (posterior lobe).
   - (c) Chromaffin tissue (suprarenal medulla).
   - (d) Sex glands.
2. Retarding (anabolic-assimilatory):
   - (a) Parathyroid.
   - (b) Hypophysis (anterior lobe).
   - (c) Adrenal cortex.
   - (d) Interstitial glands.
   - (e) Thymus.
   - (f) Pineal.
   - (g) Insular part of the pancreas.

In general, the first group stimulate the action of the sympathetic system (sympathicotrope) and the second inhibit it (vagotrope). Such relationship, however, has been demonstrated with no great certainty in the case of some members of these groups. Moreover, the development and predominance of action expressed as sympathicotonia and vagotonia, regarded as opposing forces of a physiological balance, may be the result of constitutional inferiority of one or the other system, resulting in a relative predominance of the one or the other, rather than an actual stimulation by hormonic influence. As a generalization of group correlations, little more

may with certainty be said. Of the particular relationships existing between glands and their combined action in functional activity, the following seem fairly well established.

THYROID

Thyroid-Pituitary Relation. A definite relationship is demonstrated as a result of experimental physiology and clinical medicine. The results of a very large number of investigators are in practical agreement that the pituitary shows definite and in many cases marked hypertrophy following thyroidectomy. Histological pictures indicate increased secretory activity, and the anterior lobe is the part usually exhibiting the change. Some experimental work indicates a hypertrophy of the pituitary following thyroid feeding. That the pituitary can function for the thyroid has not been proved. There appears to be no increased iodine content in the hypertrophied pituitary.

Thyroid-Gonad Relation. The relationship with the ovaries is indicated by the hypertrophy arising at puberty, menstruation and pregnancy, and by the defective and abnormal development of the generative glands following thyroidectomy and by abnormal menstrual conditions during Basedow's disease and the atrophy of the sex glands which sometimes occurs during this disease. Hypothyroidism is attended by decreased function of the gonads, frequently resulting in impotence. Thyroidectomy resulting in atrophy of testes is usually observed, but may be not a specific effect but a secondary effect, depending upon the withdrawal of the thyroid influence on general metabolism. (See Thyroid, page 48.) In the majority of cases of pregnant women, the basal metabolic rate is raised above the normal for non-pregnant women.[21] In probably the majority of cases the basal metabolic rate declines after delivery, and it has been suggested that in those in which it persists the excessive thyroid secretion gives rise to menorrhagia without pelvic signs.

Thyroid-Adrenal Relation. The effects of thyroid feeding in animals are stated by a number of workers to result in hypertrophy of the adrenals. In the case of Herring's experiments, this increase in weight amounted to as much as 56%, and there seems to be a general agreement in these feeding experiments that hypertrophy results. A few exceptions are recorded however. Thyroidectomy is reported by some to result in hypertrophy and by others in atrophy, so that it is difficult to say more than that there seems to be some kind of an interrelation between the two. This is also suggested by the experiments showing the development of an action current in the thyroid by epinephrin injection or stimulation of the adrenals through the splanchnics. Evidence of a relationship between the thyroid and the suprarenal cortex is indicated by the rapid thyroid hyperplasia after severe injury or destruction of the suprarenal cortex (W. J. M. Scott: Jour. of Exp. Med., Aug. 1, 1922, XXXVI) and the failure to obtain the increased heat production after removal of the thyroid which usually follows partial destruction of the suprarenal cortex. Removal or destruction of the suprarenal cortex in rabbits with normal thyroids usually results in increased heat production. (D. Marine and E. J. Baumann: Am. Jour.

Physiol., 59, 1922, p. 353.) From these facts it is assumed that the cortex exercises a regulatory, inhibitory or restraining influence on thyroid activity and hence on tissue oxidations. On the other hand, they believe that the thyroid and adrenal medulla mutually stimulate each other, a fact generally held and fairly well established.

Thyroid-Thymus Relation. With the thymus some relationship is evidenced by the embryology and anatomy, and by the very frequent involvement of the thymus in exophthalmic goitre, observations in various series of cases reported indicating thymus hypertrophy, a condition also often found in simple goitre. Any possible relationship is certainly far from clear.

Thyroid-Pancreas Relation. The thyroid is apparently opposed in action to the pancreas, at least in carbohydrate metabolism. The feeding of large quantities of thyroid substance depresses the secretory action of the pancreas in marked degree, although small quantities increase the secretory action.[22] (See discussion under Pituitary-Pancreas Relations.)

Pituitary

Pituitary-Thyroid Relation. (See also Thyroid-Pituitary Relation.) Pituitary feeding and the injection of pituitary extracts have been found in the experiments of various workers to cause varying degrees of thyroid hypertrophy, increase of colloid, etc. Extirpation has been reported by some to cause thyroid atrophy, and by others hypertrophy. An anti-thyroid effect of anterior pituitary claimed by some can not be regarded as proved.

Pituitary-Adrenal Relation. This relationship is suggested by the synergistic action of each upon unstriped muscle, glandular tissue and blood pressure. Some reports have appeared of hyperplasia of the cortex following pituitary feeding.

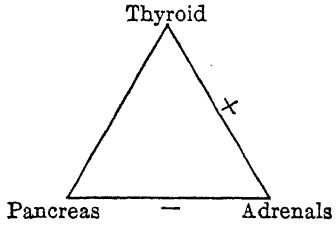
Pituitary-Gonad Relation. This is well established and is made evident from a variety of observations. There are striking changes in the gonads (atrophy) following partial ablation of the pituitary (anterior part), and the clinical evidence of atrophy of the gonads in diseases affecting the anterior pituitary is very strong.

In acromegaly there is amenorrhea in the female and impotence in the male. Pituitary feeding is reported by some to result in stimulation of the sex glands; in earlier reproduction and increased egg production in fowls. Clinically, menstrual abnormalities, amenorrhea, etc., are improved by the administration of pituitary substance.

Pituitary-Pancreas Relation. With the insular part of the pancreas the relationship is largely assumed, in view of the function in sugar metabolism. In hypopituitarism there is increased sugar tolerance, and in acromegaly glycosuria is common.

The functional relationship among the thyroid, pituitary, pancreas, adrenals and liver is evidenced in carbohydrate metabolism. The pancreas however, probably is the member of this group giving rise to a hormone action antagonistic to the others. Rudinger, Falta and Eppinger relate the action of the thyroid, adrenals and pancreas as follows: The pan-

creas inhibits the action of the thyroid and adrenals; the adrenals inhibit the pancreas and stimulate the thyroid; the thyroid inhibits the pancreas and stimulates the adrenals—relations well shown diagrammatically by Falta.



Adrenals

Adrenal-Gonad Relation. This relationship is indicated by the embryologic development; by hypertrophy (of cortex) during pregnancy and the breeding period; by hypertrophy of cortex in precocious sex development; by underdevelopment of the cortex in infantilism; by changes in interstitial cells in hyper- and hypoplasia of the adrenals; by the common association of pseudo-hermaphroditism with hyperplasia of the adrenals; by the tendency for increased functional activity of the cortex to cause the appearance of male characteristics in the female. Feeding of adrenal substance over a long period has been shown to result in hypertrophy of the ovaries and testes. Jaffe and Marine (Journal of Exp. Med., July, 1923) found that enlargement of the ovaries takes place in 76% of rabbits which survive double suprarenalectomy over 30 days. The enlargement was principally a hypertrophy of the interstitial cells.

Adrenal-Pancreas Relation. (See Pituitary-Pancreas.) The adrenals are held to exert an antagonistic action to that of the pancreas, particularly in the effects on carbohydrate metabolism. Adrenal deficiency in hypertrophy of pancreas has been noted.

Adrenal-Pituitary Relation. (See Pituitary-Adrenal.)

Adrenal-Thyroid Relation. (See Thyroid-Adrenal.)

Adrenal-Thymus Relation. The thymus is sometimes hypertrophied in Addison's disease.

Gonads

The gonads are here considered as internal secretory organs. As is well known, they comprise both the interstitial cells (Leydig's cells) and the spermatogenic cells. Between these two there is a functional antagonism (principle involved in Steinach's operation).

Gonad-Thymus Relation. The relationship seems to be one of antagonistic effect. The thymus function, most active before puberty, apparently inhibits the development of the gonads. Thymus growth and development are greatest before puberty, at which time the rapid hypertrophy of the gonads occurs and thymus involution begins. In castrated animals, the thymus is large and persists longer than in normal animals.

Increased activity of the gonads (as in the reproductive function) hastens thymus involution. This relationship in females has not been demonstrated.

Gonad-Pituitary Relation. (See Pituitary-Gonad.) In pregnancy there is an increased functional activity of the pituitary. Castration results in the hypertrophy of the pituitary (anterior) and the eosinophile cells seem to be predominantly affected.

Gonad-Adrenal Relation. (See Adrenal-Gonad.)

Gonad-Thyroid Relation. (See Thyroid-Gonad.)

Pineal

The interrelationship of the pineal and the other endocrine organs is not known. Some relationship to the suprarenal cortex and the gonads in growth and sexual development is indicated.

Thymus

Relationships unknown. Some indefinite relation to the thyroid is suggested.

PLURIGLANDULAR THERAPY

As physiological investigation and experimental pathology more and more supplemented the observations of clinical medicine, the interrelationship of the endocrine glands became firmly established. Many of the fundamental facts relative to this relationship are stated above, under the detailed consideration of this subject. As the field developed and the practical application to therapeutics, organotherapy, began to receive a more careful study, it became evident that this fundamental fact of endocrine interrelationship would have to be taken into account in therapy as well. There was increasing evidence that a substantial percentage of the cases of failure to obtain results were due to failure to combine gland substances in prescribing, and that in such cases other causes of failure, faulty diagnosis, inert gland products, etc., could be excluded. The experience of Bell was similar to that of many other workers in this field:[23]

> "In seeking to discover the reasons of the uncertainty of action of the ovarian extract, I found that this preparation is much more active when thyroid extract is administered at the same time."

Scientific Basis for Pluriglandular Therapy

The underlying principle of pluriglandular therapy, therefore, is rational and based upon considerations and facts which should convince the most exacting. In general it rests upon the established facts of a physiological endocrine interrelationship, the recognition of endocrine diseases as pluriglandular conditions, and by an extension of this thought now thoroughly demonstrated, upon the synergistic effects exhibited by the gland substances used in therapy. Pluriglandular therapy followed as a logical and necessary step the recognition of the facts just related. The organotherapy of ancient medicine, and in fact until very recent time, was one making use of single glands alone, and we have observed the failures resulting.

"Uniglandular organotherapy had its rise when clinical and experimental observation disclosed the phenomena which result from alteration or extirpation of one or another glandular element, failing to take account for the most part of the anatomical and physiological connection between these elements. But when their complete functional unity and intimate biological connection came to be understood, their morbid manifestations ceased to be looked upon as due to separate factors and treatment became directed with a view to their physiological interrelation, the only method of dealing fully with their functional insufficiencies."[24]

Direct quotation from some contemporary sources will give evidence of the general acceptance of these views. The first group of five given below relate particularly to endocrine disturbances as pluriglandular, and the last group of seven to the efficiency and desirability of pluriglandular therapy.

Group One *Statements relating to endocrine disturbances as polyglandular:*

1. "It should be recognized that when one gland is malfunctioning others are also disturbed, and may thus cause atypical conditions." (Osborne: Principles of Therapeutics, 1921, Part 4, p. 400.)

2. "That the various structures making up the endocrine system stand in intimate functional relation with each other has become a medical truism." (R. G. Hoskins: Endocrinology and Metabolism, 1922, Vol. II, p. 919.)

3. "When one considers the interrelation and interdependence of the units of the internal glandular system, it is hardly conceivable that there should be any absolutely uniglandular disturbance." (Walter Timme: Endocrinology and Metabolism, 1922, Vol. II, p. 883.)

4. "The most remarkable fact about the internal secretions is that they are correlated with one another. Not only has it been abundantly demonstrated by experiment but in many cases pathological lesions of the individual glands cause some disturbance in the functional relations of other glands—the so-called 'pluriglandular syndromes.'" (Fielding H. Garrison: Endocrinology and Metabolism, 1922, Vol. I, p. 70.)

5. "The theory of a correlation between the glands that constitute the endocrine system though only vaguely understood is, nevertheless, essentially well established. It may be stated in general that the ductless glands are normally so correlated as to form a perfect physiologic balance which is preserved by a proper distribution of harmony and antagonism between the functions of the various glands. If one of the glands is diseased or injured or extirpated the normal balance is upset and the organism of the individual may be affected by the abnormal action of one or more distant glands of the group." (Graves: Gynecology, 2nd Edition, 1921, p. 45.)

Group Two *Statements relating to pluriglandular therapy:*

1. "I believe that the future development will be along the line of pluriglandular therapy, due to the probable correlation between the pituitary, thyroid, mammary gland, suprarenal and ovary, rather than in the use of single extracts." (J. C. Hirst: New York Medical Journal, October 5, 1921.)

2. "It is possible that the reason why physiologically active secretions of various organs, such as the ovary, the suprarenal cortex and the anterior lobe of the pituitary, have not been obtained and utilized therapeutically is because they do not produce their effects single-handed; they must either be activated by or combined with some other substance, as they are normally in the body, before they can give effect to any properties they may possess. We have direct evidence of this in the activity of the implantations of the structures mentioned as opposed to the inactivity of their extracts." (Blair Bell: The Pituitary, 1919, p. 179.)

3. "In the same way as I have built up a pluriglandular theory, I have associated the glandular extracts to the point of almost entirely eliminating from my materia medica monoglandular therapy." (A. G. Abadal—La Semana Médica, May 13, 1920.)

4. "On *a priori* grounds, however, if endocrine syndromes are, as many maintain, always or even commonly pluriglandular, more rapid amelioration might be expected if a suitable pluriglandular formula were used. Practically, rational pluriglandular therapy would seem to demand a large number of different combinations and these in different proportions in each case, as indicated by the degree of involvement of each gland and the susceptibility of the patient." (R. G. Hoskins: Journal American Med. Asso., July 8, 1922.)

5. "I have already insisted too much on the importance of polyglandular syndromes and the frequency of a simultaneous alteration of several glands, to say more on this subject. We must oppose an associated organotherapy to multiple functional disturbances. In some cases, it is best to give each one for a certain period, in other cases the extracts of various glands should be given simultaneously. I find more and more that I have to use preparations containing a combination of thyroid, pituitary, ovarian and adrenal in varying proportions. When administered in syndromes, such as Dercum's disease, glandular obesity, sclerodermia, certain cases of infantilism, etc., these organotherapeutical preparations seem to act very favorably. It even seems as if thyroid medication was better tolerated when combined with either adrenal or pituitary extract. When medication has to be carried out for a long period of time the association of these extracts is particularly indicated." (P. Lereboullet: Endocrine Glands and the Sympathetic System, p. 50.)

6. "The conception of pluriglandular syndromes has a practical interest: the application of mixed organotherapy in their treatment. Rénon has insisted on the successful results which may

be obtained by a mixed organotherapy which would fail if only one gland was used. As an illustration, we will recall the use of thyroid-ovarian medication in ovarian insufficiency." (P. Harvier: Endocrine Glands and the Sympathetic System, p. 250.)

7. "We have previously referred to associated insufficiencies of several organs, particularly of several endocrine glands. In these cases, it is perfectly legitimate to use several extracts. It is possible to obtain preparations of different extracts in the proportions in which they are best given." (H. Carrion: Endocrine Glands and the Sympathetic System, p. 364.)

The first systematic presentation of the arguments for combining gland substances appears to have been made by Rénon and Delille in 1907. In this same year also the term pluriglandular syndrome was suggested by Claude and Gougerot. Making use of the data at that time available relating to the interrelationship of the glands, they reported that in applying these ideas to opotherapy, after many experiments, they "succeeded by means of a mixed medication, thyro-ovarian, ovaro-hypophyseal, etc., in controlling diseases which had not yielded to one medication alone, thyroid alone, ovary alone, etc." French medicine has perhaps taken the lead in recognizing these principles, which must be considered in physiology, therapeutics and diagnosis.

Pluriglandular Theory in Diagnosis and Clinical Medicine

In France there have been developed rather comprehensive classifications of syndromes, based upon the clinical phases, but related to the endocrine glands involved. In a recent work[25] pluriglandular syndromes are divided into three groups as follows:

First Group. This is characterized by a primary alteration of one gland and a secondary action on several others. There is always a predominance of one gland in the symptomatology of the disturbance. Under this heading are included (1) pluriglandular syndromes with thyroid predominance, (2) pluriglandular syndromes with pituitary predominance, (3) pluriglandular syndromes with ovarian predominance.

Second Group. This group is made up of an association of two uniglandular syndromes, the peculiarities of each being discernible. This includes such conditions as exophthalmic goitre associated with Addison's disease or acromegalia, myxedema following Basedow's disease, myxedema with acromegalia.

Third Group. This is characterized by the association of the several uniglandular syndromes without predominance of any particular gland.

A classification of a somewhat similar kind is also found in Laignel-Lavastine's "Internal Secretions and the Vegetative Nervous System." They are of interest here, not only as helpful schemes in diagnosis but to give additional emphasis to the recognition of the pluriglandular character of endocrine disturbances.

In those conditions which are intimately and directly related to particular endocrine glands, such as dysmenorrhea with its immediate relation-

ship to the ovary, we find examples in the current practice of general recognition of these principles in combining glands in therapy, even though the clinical syndrome points to involvement of a single gland. The following are examples:

> "In gynecologic practice, extracts of the whole gland are indicated in menstrual disorders that are essentially the result of pituitary deficiency, in which cases ovarian therapy may be used in combination." [26]
>
> "In primary dysmenorrhea, however, we have to deal with a developmental defect—a uterine hypoplasia—which is assuredly of endocrine origin. The indication for organotherapy is a real one. Extracts of the entire ovary are here indicated, in combination with anterior pituitary substance and often with thyroid." [27]
>
> "In ovarian insufficiency of all types, congenital, menopausal, nervous or congestive, combination proves far more efficient for certain cases of uterine dysmenorrhea than ovarian medication alone." [28]

The recognition of this principle may be also noted in the statement of Harvey G. Beck,[29] in referring to syndromes referable to disturbed pituitary action:

> "Another difficulty formerly encountered was in grouping these cases. Many of them present pluriglandular manifestations which result from the reaction and interaction of the chain of ductless glands—notably the thyroid, sex glands and adrenals. They frequently have a genital syndrome which may be primary or secondary, and symptoms referable to thyroid and adrenal insufficiency. In the writer's series of 46 cases, 27 showed symptoms of varying degrees of hypothyroidism. De Camargo makes the broad statement that there is no such thing in pathology as a monoglandular syndrome, for all endocrine syndromes are pluriglandular with predominance of one gland. Consequently, a combination of the respective hormones, especially thyroid and pituitary, should yield better results in this class of cases than either one given singly."

Abadal also developed pluriglandular therapy from the standpoint of pre-eminence of the adrenal chain as the controlling influence in the animal organism. He summarizes his views as follows:

> "1. Polyopotherapy is the logical corollary of our knowledge of the physics and chemistry of the great endocrine group comprising the pituitary, the thyroid, the parathyroid, and the adrenal glands.
>
> "2. In every insufficiency of this group, even when a given element seems to predominate, polyopotherapy is more effective than the administration of the secretion of that gland alone which we believe to be the prime factor in the syndrome.
>
> "3. The association of the pituitary with the other glandular extracts, thyro-ovarian, testicular, etc., increases their activity.

"4. Whole pituitary, when combined with thyroid, increases its tolerance, allowing us in cases of thyroid insufficiency finally to reach toxic amounts without, as a rule, observing the phenomena of therapeutic hyperthyroidism.

"5. The amount of extract to be administered in polyopotherapeutic treatment is the same as is usually employed in monoglandular insufficiencies, increasing or diminishing the amount according to clinical indications in the case of each individual gland."[30]

It will be evident from the discussion of the subject that pluriglandular therapy has nothing whatever in common in theory with the "shot-gun" therapy of a bygone day. "Shot-gun" therapy arose primarily as a result of the failure of diagnosis, and with a profound ignorance and disregard for chemical and physiological incompatibilities proceeded to combine drugs of various descriptions, in the pious hope that some one would accomplish the desired effect. Any superficial similarity to combining glands in therapy appears to lie solely in the use of more than one gland product in the same prescription. We have noted in organotherapy, even when the diagnosis recognizes the overwhelming predominance of a particular gland in the syndrome, that, for reasons both theoretical and based upon clinical observation, appropriate synergistic glands are included in a pluriglandular prescription.

Dosage Dosage of endocrine substances will be described under the several glands. The preparations are generally prescribed on the basis of the desiccated substance, although there are products on the market in which the grain dose refers to fresh gland substance. Such a system has no place in medical practice today. Such products as the milk and serum of animals in which various glands have been removed are not in general use today.

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PART II

CHAPTER I

THE THYROID GLAND

ANATOMY

The human thyroid is made up of two main masses, the lateral lobes, joined by an isthmus, the combined portions having a weight of about 30 to 35 grams. It lies in the middle of the neck and partially covers the trachea and large vessels and nerves. The gland is enclosed by a capsule which maintains it in position and is of interest surgically. The capsule is connected with the fascia of the neck and is described as like the peritoneum in structure. From it septa extend into the gland, forming the thyroid lobulations. In addition to the capsule proper, there is an outer or false capsule intimately connected with the fascia of the muscles of the neck. Accessory lobes or thyroids are frequently encountered. These may extend from the root of the tongue to the arch of the aorta, and account for the occurrence of goitre in these unusual sites (substernal goitre), etc. The thyroid is covered superficially by the skin, fascia, infrahyoids and platysma muscles, and the lobes can ordinarily be palpated without difficulty. This is not true of the isthmus, which is usually small and in a plump, thick neck defies all efforts at palpation. In some persons without hypothyroid symptoms, and especially in hypothyroid cases in school children, etc., the lobes themselves can not be outlined.

BLOOD SUPPLY

The thyroid is one of the most vascular of all the organs, and it has been stated that the entire volume of blood in the dog passes through the thyroid sixteen times a day. This remarkable blood supply is through the superior thyroid arteries on each side above and the inferior thyroid below, and the anastomoses between them. The larger arteries in the septa have well-defined walls which become less distinct as they grow smaller, and finally form a capillary network around the thyroid acini. A network of veins carries the blood through the superior, middle and inferior veins of the jugulars and the left innominate. The thyreoidea ima artery is said to be present in about 10% of cases and arises directly from the arch of the aorta; a corresponding vein when present empties into the left innominate.

NERVE SUPPLY

The nerve supply has never been satisfactorily determined. The branches of the sympathetic probably constitute the chief supply, and this may be supplemented by the superior, inferior and recurrent laryngeal. The secretory function of the sympathetic has, however, been questioned by

many. Cannon, Ringer and Fitz [1] reported that fusion of the central end of the phrenic to the peripheral end of the cut sympathetic gave continuous stimulation to the thyroid and resulting hyperthyroidism. Marine, Rogoff and Stewart,[2] Mills,[3] H. B. Vandyke [4] and Burget [5] failed to demonstrate such secretory activity. The sympathetic fibres arise from the first and second cervical sympathetic ganglia and follow the course of the arteries—principally inferior thyroid—into the substance of the gland. The fine network of nerve endings around the alveoli is probably sympathetic, and the experiment of uniting the phrenic with the cervical sympathetic, with the development of hyperthyroidism, supports this view. In this experiment there is practically continuous stimulation passing down the phrenic through the sympathetic. Lying in the meshes of the network formed by the septa from the capsule lie the acini, the active functioning parenchyma of the gland. They are usually described as lying upon the connective tissue network without the intervention of a basement membrane. There is a great diversity in both size and shape of the follicles, as well as in the character of the epithelial cells lining them. In the cavities of the acini is found the colloid material characteristic of the thyroid. This stains with eosin and is attached by fine filaments to the acini. In normal specimens it usually occupies the entire alveolar cavity. Vacuole formation, however, is common. The shrinking of the colloid substance is generally believed to be due to imperfect fixing. It is the colloid which contains the iodine bearing compounds believed to represent the internal secretion. Lying in the connective tissue stroma, between the follicles, are found groups of epithelial cells, with no apparent formation into organized structures. They apparently do not differ in form from the epithelial cells of the acini, and are of importance through their giving rise to interstitial adenoma. These cells are not constant in number or site. It is stated by some (Hertzler) that in these masses of interstitial cells colloid collects and new acini are formed. Hertzler notes changes of these cells in the "Forme Fruste" type of goitre, while others find such changes in exophthalmic goitre. In interpreting histological specimens of thyroid, however, it should be remembered that there is no established normal type. Variations, due to physiologic, individual, regional, seasonal and other factors, are common and give essential differences in the picture.

Embryology

The thyroid develops as an evagination from the entoderm of the floor of the pharynx, between the first and second branchial pouches. The first structure is a solid column of cells which divides into two lateral portions, and the whole structure becomes hollowed out—a process said to be independent of the original hollow of the pharyngeal pouch. The original lateral branches continue to subdivide and form a system of hollowed out tubes lined with epithelium, and which as development proceeds become closed off to form the thyroid acini. These acini later become filled with the colloid material. The open median column, as it becomes elongated, is the ductus thyreoglossus—a duct which persists in some lower orders. It persists in man up to about the eighth week. The colloid begins to form in appreciable amounts only after birth.

PHYSIOLOGY

The thyroid gland, without any question, elaborates an internal secretion which exerts most profound effects on the growth and metabolism of the body. Its function as a detoxicating organ is probably dependent upon its general effects on metabolism—while its function, as stated by some authors, in connection with sexual development, is a part of its general influence on growth. The thyroid bears an important relation to immunity processes, however, and it is well known that thyroidless animals are more susceptible to infection. This is not believed by some, however; thus Ecker and Goldblatt [6] find that "thyroidectomy with partial parathyroidectomy does not inhibit anti-body production." Koopman [6a] with a different method of experimentation comes to an opposite conclusion. Hammett's [7] studies on thyroidectomized and partially thyroidectomized rats show that removal of the thyroid does not interfere with conception, and does not apparently inhibit the function of the internal secretion of the gonads in the development of secondary sex characteristics, stimulation of sex activity or the preparation of the uterine mucosa for nidation. Certain other processes of reproduction, however, were influenced, but these appeared to be due to a general lowering of the anabolic level as a result of the lack of the thyroid stimulus to metabolism in general, rather than a lack of any specific influence on the reproduction process. The thyroid effects are probably reflected in all active cells of all tissues and are in general catabolistic—accelerating metabolism and speeding up the activity of the cell. Most of the effects are doubtless due to the active iodine compound described below—thyroxin. The iodine in this compound and in other compounds in the thyroid appears to act as a catalytic agent in metabolism. "It would appear that the study of the thyroid begins and ends with iodine. Marine states that simple goitre and the incidence of fetal adenomata result from a deficiency of iodine alone. On the other hand, goitres of the exophthalmic type are due to hyperiodism—the hypersecretion of thyro-iodine by the thyroid. The excessive iodism causes abnormal permeability of the cell membranes. Increased permeability of the cells means increased activity. Increased activity of the cells—increased metabolism—is one of the results alike of iodism and of stimulation." [8] The effects of thyroid iodine, according to Crile, are electrochemical and the organism is an electrochemical mechanism, in which the thyroid regulates the electric conductivity. Some interesting experiments have been made to show that the electric conductivity of the brain of animals is increased in acute iodism.

The thyroid is indispensable for normal growth and development of the organism. In cases of atrophy of the gland, such as occurs in cretinism, the failure of physical and mental growth is manifest. Here growth fails almost completely, ossification fails, mental growth fails to take place and the whole process of growth and development comes to a standstill. These results are also produced in animal experimentation. The result of thyroid feeding and the administration of thyroid derivative to such cases is one of the most astounding in medicine. Growth is accelerated, the mental development proceeds, and, if instituted early, the development and growth of the

organism may proceed approximately along normal lines. Thyroid thus administered stimulates growth and development in all classes of tissue—even in the tissue of lower forms not possessing a thyroid. The effect of thyroid feeding on the growth of normal animals is somewhat uncertain—some holding an acceleration and others a retardation. The results of A. T. Carmichael and J. Carmichael [9] are of this latter class. They found that without exception thyroid feeding over a long period of time is attended by a marked decrease of growth rate. This, however, has no significance in the consideration of those cases in which there is a lack of thyroid hormone—hypothyroidism—in which definite stimulation of growth is the rule. The nature of this action of stimulation of growth and development is unknown. It may be the same action which is exerted in metabolism—catalytic effect—in which inherent tendencies in the organism, which would proceed without it, are simply speeded up.

The thyroid is interrelated with other endocrine organs in the regulation of the process of menstruation, and during pregnancy the thyroid hypertrophies, to compensate for the added functional requirement, and some hypertrophy at the time of the menstrual period and at puberty is not uncommon.

The thyroid appears to be more fundamentally related to the female organism and sex apparatus than to the male. In experiments by Hammett [118] on young rats, thyroidectomy caused marked loss in development of the ovary and uterus and loss in weight, while in males growth of the testis and epididymis was not greatly retarded. From these experiments it is concluded that not only the growth, but also the functional activity, of the reproductive system of the female is very intimately related to the thyroid function, and that this more intimate relation of the thyroid to the female sex glands is responsible for a greater occurrence of thyroid diseases, particularly of goitre, in the female.

Extirpation Experiments

The earliest experiments in removing the thyroid, for various reasons, led to no certain conclusions, although the general consensus was that the gland was highly important in the normal physiological function, and perhaps indispensable to life. Some of the uncertainty was due doubtless to the variability of the operative procedure and to the removal of the parathyroids. The age of the animal was also neglected in the earlier experiments. It has been shown that this is very important, as it has been demonstrated that the effects on animals at different ages give very different results. As early as 1856 Schiff showed that removal of the thyroid in dogs is fatal, but he abandoned this work and little or no attention was paid to it. Following the work of the Swiss surgeon, Kocher, and of Reverdin in 1884, he repeated his experiments and described the symptoms resulting. His observations have since been confirmed by many observers, and none would now deny the tremendous importance of the thyroid. It may be regarded as the opinion of practically all observers today that extirpation of the thyroid in dogs, monkeys, and all animals in which there are no well developed accessory masses of thyroid tissue will either result in death or the production of cretinism or myxedema with

most of the symptoms described elsewhere under these titles. In general, there is dry, thickened, scaly skin, tendency to adiposity and myxedematous infiltration, low temperature, low metabolic rate, dullness, dwarfism, lowered sexual capacity and loss of hair.

Suprarenal cortex extirpation is attended by striking changes in the heat production and CO_2 output, and the changes seem to be definitely related to the thyroid.[10] It is suggested that the increase of heat production following removal or injury to the suprarenal cortex is due to a normal restraining influence of the cortex on the thyroid. "The thyroid and suprarenal cortex are antagonistic while the thyroid and chromaphil tissue, as the work of previous observers have indicated, mutually stimulate each other." The symptoms of thyroid removal itself are generally regarded as referable to disturbance of the metabolic and growth functions, whereas the symptoms of irritability, tetany, etc., are due to the removal of the parathyroids. The condition resulting from thyroid removal in man is called "cachexia strumipriva." It should be remembered that the thyroid is more important to some classes of animals than others. Thus, the quiet, placid herbivora are not nearly so much affected by extirpation as carnivora, in which the symptoms are usually severe.

Feeding Experiments

Among the best known experiments are those of Gudernatsch in feeding thyroid substance to tadpoles. He noted that metamorphosis was markedly accelerated and that there was a pronounced tendency to tissue differentiation. The metamorphosis into the frog was greatly hastened over that of the controls, but further growth appeared to be hindered. These results have been confirmed by other observers in practically all details. The result obtained by Cooksey,[11] with especial reference to the effect of thyroid feeding on the brain of tadpoles, is of interest in connection with the effects of the thyroid in normal mental development. He says:

> "These facts show that thyroid feeding greatly accelerates the development of the brain, causing it to assume adult characteristics in a comparatively short time, as is clearly shown, for example, by the shortening of the diencephalon, which averages 40.65%, and the decrease in the width of opening of the fossa rhomboidalis, which averages 38.4% in tadpoles fed only 7 to 11 days." * * * "In all parts of the brain of the thyroid fed tadpoles, adult characteristics were evident. The body length decreased 15.89%, while the brain length increased 1.76%."

While these experiments may show nothing more than the acceleration of normal metamorphosis, it is significant that the development of adult characteristics in the brain is apparently selectively furthered. Thyroid feeding in other animals has given varying results, but in large dosage there is usually increased nitrogen excretion, loss of weight and general stimulation of nitrogen metabolism.

Cameron and Ledziak[30] found that thyroid feeding in the case of white rats caused hypertrophy of the heart, liver, kidneys, adrenals, spleen and lymph glands. These results were evident in 18 days. The thyroid

gland itself enters into a resting position, muscle tissue wastes and fat disappears. These results are in agreement with those of Hoskins, Herring, Cameron and Carmichael, and emphasize the parallelism of hyperthyroidism and the clinical manifestations of heavy thyroid doses.

The action of the thyroid hormone has been stated, therefore, to be one of simple stimulation of cell metabolism, and nothing more. Thyroid "stimulates metabolism like a bellows fans a fire." (von Noorden.)

Mechanism of Thyroid Action

The mechanism whereby this increased metabolism is effected is probably a direct catalytic effect on the cell chemistry, and not through any indirect means. In a series of experiments by Aub and his associates [12] upon the mechanism of the increased metabolism in hyperthyroidism, they found that

> "It has, therefore, been satisfactorily proven that the increased metabolism due to the administration of thyroxin is maintained in spite of the elimination of all muscular activity of the limbs and in spite of the removal of tonus from these muscles. The adrenal glands are also not essential to the maintenance of the high metabolism. We are, therefore, again confronted with the theory that the thyroid secretion acts as a draught, stimulating the resting body cells to an increased rate of combustion."

Willier's experiments (Am. Jour. Anat., Mar., 1924) strongly indicate the passage of a thyroid hormone directly into the blood and with no nerve mediation. Thyroid grafts produced in the host embryo, emaciation, atrophy of internal organs, etc. Catabolism was increased over anabolism.

It has been stated (Kendall) that it is not essential to life, but is a catalyst which merely influences the chemistry of metabolism. Such an action is evident in the experiments of Carrell, who found that tissues cultivated in vitro grow several times as rapidly when thyroid substance is added to the extract. The effect of the amount of thyroid administered, however, is all important. Thyroid hormone acts as an accelerator of metabolism, and in large quantities the metabolism is so speeded that nitrogen loss occurs with loss of body weight. Here the catabolism has been so rapid that body tissue has been drawn upon to replenish the waste, and anabolism has been impossible. But in small doses thyroid may cause actual nitrogen retention and increase the body weight. Experiments quoted by Janney are convincing on this point: [13] "Recent experiments by Schaeffer and Hewitt have afforded valuable data. These authors fed thyroid glands to white mice in varying amounts and studied the nitrogen metabolism and body weight. The following condensed tabulation has been compiled and calculated from Hewitt's second article. The experiments were evidently carefully carried out and the fecal nitrogen was also controlled. From the tabulation it is evident that the amount of thyroid gland administered determines its effect on metabolism. The effect of 0.25 gram daily in the second week caused a slight loss in body weight with a decided decrease in the nitrogen retained. In other experiments the feeding of 0.5 and 1.0 gram under the same conditions led to still greater loss of weight and nitrogen. When, however, 0.125 gram daily was administered more food and nitrogen were ingested than under normal dietary conditions, or when a large amount of gland was fed.

HEWITT'S THYROID FEEDING EXPERIMENTS

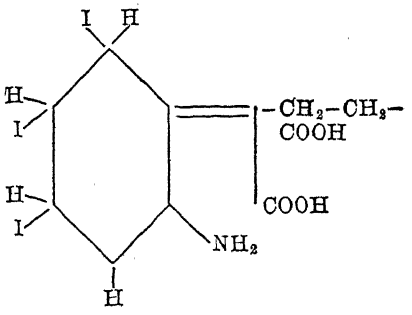
Week	Diet	Food per kg. gm.	Nitrogen intake per kg. gm.	Nitrogen in urine per cent	Nitrogen retained per kg. gm.	Gain or loss in weight per cent
1	Normal period	264	2.66	1.55	1.367	7.0
2	0.25 gm. oxythyroid daily	253	2.58	2.06	1.14	1.7
3	0.125 gm. oxythyroid daily	305	3.36	2.09	1.61	10.4
4	0.25 gm. oxythyroid daily	304	3.20	2.11	1.35	3.3

"The urinary nitrogen remained stationary. It is, however, very significant that 18% more nitrogen was retained than in normal patients and that the body weight increased 10.4%, corresponding to about 50% over and above the total increase noted in the normal period in the same length of time. * * * Hence it is evident that all therapeutic action of the thyroid should be found to be accompanied by a gain, not a loss, of nitrogen." The continued administration of large doses of the iodine compound, thyroxin, in man is attended by rapid, irregular pulse, flushing of the skin, tremor, sweating, loss of weight, nervous excitability, greatly increased metabolic rate and nitrogen loss. The value of these observations in therapy is manifest in combinations used for "tonic" effects. Probably less than one grain daily, or more nearly ½ grain, of desiccated thyroid extract is desirable.

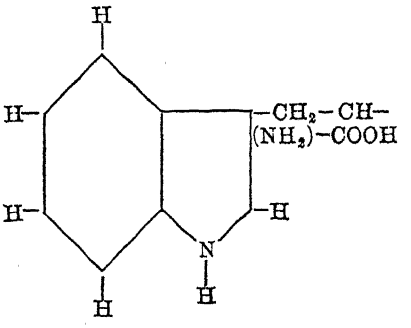
The Active Principle of the Thyroid

It is well established that the normal effect of thyroid is due to the iodine bearing compounds elaborated by it. This function of fixing iodine appears to be characteristic of thyroid, and it is generally held that the activity of the thyroid and of thyroid preparations is dependent (in direct proportion) upon its iodine content. The U. S. P. standardization is based upon the iodine content requiring from 0.17 to 0.23%. The iodine is held in the thyroid in organic combination, the largest single constituent being the compound iodo thyro-globulin, which may be present in an amount equal to one-half the weight of the desiccated thyroid. It is shown by some experiments to give all the effects of whole dried thyroid therapeutically. Iodo thyrin is a substance first described by Baumann and of doubtful constitution. Some observers believe it is obtained by hydrolysis of iodo thyro-globulin, and little mention is now made of it in the literature. The substance, however, which has attracted the most attention is thyroxin, believed by many to represent the active physiological principle—the hormone of the thyroid. Thyroxin is obtained from thyroid substance or from iodo thyro-globulin, and the formula as determined by Kendall[14] is 4-5-6 trihydro, 4-5-6 tri-iodo—2 oxybeta—indol proprionic acid, a formula verified by Osterberg, who is stated to have synthesized it. It occurs in three stereoisomeric forms, a keto form, an enol form and as a molecule with an open ring, which is believed by Kendall to be the form occurring

in the body. It has a general resemblance to tryptophan and is described as a tryptophan derivative. It contains 65.1% iodine and has a molecular weight of 585.



Thyroxin (open ring form)



Tryptophan

Thyroxin Thyroxin occurs only in the thyroid colloid. It is believed by Kendall that the oxyindol nucleus is largely responsible for the physiologic activity in stimulating metabolism, rather than the iodine. If the H in the imino group is replaced by acetyl, the activity is lost. However, the iodine substituent must be of large importance, and Kendall regards it as an activator. Kendall states:[35]

> "Patients with complete atrophy of the thyroid have basal metabolic rates approximately 40% below normal. It has been shown that administration of thyroxin alone can bring back and maintain the normal metabolic rate in such patients. But in complete atrophy of the thyroid the complete or nearly complete absence of thyroxin may be assumed. The question arises as to what maintains energy output from 100% below normal, which would be death, up to 40% below normal, the point to which basal metabolism sinks in the absence of thyroxin. May it not be the other chemical substances in the body possessing the same grouping that occurs in thyroxin? These are amino acids and protein, creatin and creatinin and a few other less well-known compounds. It seems probable that on the administration of thyroxin a reaction which has been carried on within the body by other compounds is merely increased in rate, but that there is no difference or disturbance of the reactions that have been going on."

The action of thyroxin is, therefore, believed to be catalytic, and in experiments it appears to act in this way, being used for as long as 21 days by the body before final destruction or inactivation (poisoning) of the catalyst. In some animal experiments iodine alone is sufficient to change the metabolism. Thyroxin affects the blood pressure, pulse rate and metabolism—first the nitrogen metabolism, then the fat. Increased carbohydrate metabolism may be due either to direct stimulation or indirect effects One milligram of thyroxin increases the metabolic rate about 2%.

> "The effect of one milligram of thyroxin, given intravenously, is an increase in the basal metabolic rate of 2.8 points; * * * Thyroxin undoubtedly has a specific dynamic action,

increasing the metabolic rate in proportion to the quantity actively present in the body. Kendall has suggested the probability that its specific action lies in aiding oxidation by rendering more readily available nascent oxygen atoms which agrees with the theory of Plummer, that the active agent of the thyroid gland is a catalyst that accelerates the rate of formation of a quantum of potential energy in the cells of the organism." [16]

A peculiarity of the action of thyroxin is the delay before the effects have become manifest. These usually do not follow until after a lapse of from 24 to 36 hours. The height of the reaction may occur on about the eighth day.[17]

> "After reaching the maximum effect thyroxin still continues to function for another eight or ten days, so that the length of time a single administration of thyroxin functions within the body is about three weeks."

Less than one milligram daily will replace the loss of thyroxin in the body, and this is sufficient dosage. For oral administration, due to incomplete absorption, the dose is about $1\frac{1}{2}$ milligrams ($\frac{1}{4\frac{1}{3}}$ grain) daily. It is not proven that thyroxin is the sole active internal secretion produced by the thyroid. It contains about $\frac{1}{4}$ of the iodine of the gland. The remaining $\frac{3}{4}$ is iodo thyro-globulin and other organic combinations, and these also have some physiological activity. Experiments by Hunt [18] with thyroid and thyroxin in the very delicate aceto nitril test for thyroid activity in mice show that "the physiological activity of thyroxin, both by feeding and by intravenous injection, is (expressed in terms of iodine content) less than that of thyroid." It may be that thyroxin is a true end product of iodine synthesis and represents the part actually thrown into the blood in normal conditions. However, little is definitely known on this point and some of the experimental work[19] would indicate that the active constituent actually leaves the thyroid through the lymph as iodo thyro-globulin. This was determined through precipitation tests, the iodo thyro-globulin having been shown to act as an antigen. The failure to demonstrate the substance in the blood, however, does not eliminate this mode of entrance to the body as the experimenters themselves point out. In therapeutics there is also some difference of opinion, although some writers state that thyroxin produces all the effects of thyroid administration. "When thyroxin is given to a myxedematous patient all the symptoms, due to myxedema, are promptly relieved. When it is given in too large amounts hyperthyroid symptoms are produced." [20]

HYPERTHYROIDISM

Dysthyroidism

Hyperthyroidism is a term that requires a great deal of explanation, for the reason that it is variously conceived and defined, and because the generally held definition, making hyperthyroidism a synonym for exophthalmic goitre, is essentially different from the prefix hyper in such conditions as hyperpituitarism, hyperadrenalism, etc. In this use hyperthyroidism is used to describe a condition and a syndrome believed by many to be much

more than the mere effects of excessive thyroid secretion in the organism. If exophthalmic goitre were due simply to excess thyroid principle in the blood, it should be possible to produce the condition by excessive thyroid administration. The great majority of opinion holds that this has never been done. Hyperthyroidism experimentally produced certainly is not the picture of exophthalmic goitre. Some authors maintain, however, that practically all but the eye symptoms may be produced by feeding large amounts of thyroid material. Falta states that the following may be produced:

Experimental Hyperthyroidism

(1) Tachycardia;
(2) Great depression of blood pressure;
(3) Increase of basal metabolism;
(4) Increase of protein metabolism;
(5) Increase of elimination of solids;
(6) Lowering of the assimilation for carbohydrates and finally spontaneous glycosuria;
(7) Sweats;
(8) Mononucleosis;
(9) Tremor;
(10) Diarrhea;
(11) Psychic agitation.

Falta states, however, that almost never are all these symptoms produced at the same time or in a single individual, but that tachycardia is the only constant symptom to which some of the other symptoms are added in different cases. But this, it would seem, is not producing Basedow's disease. The exophthalmus is never produced, the tremor and nervous symptoms are inconstant, and states of hypothyroidism which frequently attended Basedow's can not be reconciled with this theory. Administration of thyroid extract sometimes improves Basedow's disease. The toxic element in Basedow's has suggested the theory of dysfunction. Janney has suggested that in the synthesis of the thyroid hormone there may be a defect which permits partly or improperly synthesized products to enter the blood stream instead of the fully formed normal principle. These products are toxic and give rise to the characteristic toxic effects. This would also explain the hypothyroid effects frequently encountered because of the decreased production of the normal, fully formed, hormone. It would account for such hypothyroid symptoms as fatty heart, brittle, scanty hair, myxedema of the skin, goitre, mononucleosis, etc., as well as the fact that the goitre of Graves' disease contains only as much as $\frac{1}{50}$ the iodine content of the normal. Falta does not believe in such an "intoxication theory." "The expression poisoning is, according to my opinion, well adapted in many diseases due to hyperfunction; for example, in Basedow's disease. On this account, we do not need to assume a dysfunction, as a normal secretion too, given in excess to the body, may poison it."

Dysthyroidism

Plummer distinguishes between the hyperthyroidism of Basedow's and that of toxic adenomatous goitre, differences which now receive rather general recognition. These are described by W. M. Boothby as follows:[11]

"1. According to Plummer's classification there are two separate and distinct types of hyperthyroidism, each due to a different pathologic change in the thyroid gland: in the one type, the hyperthyroidism associated with the clinical syndrome of true exophthalmic goitre is always accompanied by diffuse hypertrophy and hyperplasia of the thyroid gland, in the other type the hyperthyroidism, not associated with this typical diffuse hypertrophy and hyperplasia, but with the occurrence of adenoma in the gland, is due to the adenoma, and the resulting clinical syndrome is distinguishable from that occurring in true exophthalmic goitre.

"2. The syndrome associated with the hyperthyroidism from adenoma of the thyroid is considered by Plummer to be a distinct clinical entity and may be defined as a disease associated with adenoma, characterized by an increased basal metabolic rate excited by an excess of the normal thyroid hormone in the tissues. About middle age the adenomatous tissue gradually begins to furnish an excessive amount of the apparently normal thyroid hormone (thyroxin) and this produces the increased metabolic rate and intoxication clinically evidenced by nervousness, tremor, tachycardia, loss in strength and weight, and a tendency to hypertension, and in the later stages myocardial disintegration. The underlying cause or stimulus that activates the thyroid to adenomatous growth and over-secretion is not known."

EXOPHTHALMIC GOITRE

Hyperthyroidism, Graves' Disease, Basedow's Disease, Flajanis' Disease, Parry's Disease

This condition was described in 1835 by Graves and in 1840 by Basedow, who described the three cardinal symptoms of goitre, exophthalmus and palpitation of the heart—the "Merseburg triad." Parry, of England, before his death in 1825, had however fully described the condition and noted, in addition to the three signs of the triad, the symptoms of nervousness and tremor. The definition of Falta is comprehensive and seems the best yet formulated.

> "By Basedow's disease we understand today a disease which is brought about principally by the abnormally increased activity of the thyroid gland. This is almost always accompanied by an enlargement and increased vascular engorgement of the thyroid gland, and leads eventually through the local symptoms conditioned by the enlargement to a great number of very manifold manifestations, of which especially the tachycardia, the well-known eye symptoms, the tremor and the increase in metabolic processes are the most important. Most of the manifestations are to be explained by a heightened condition of excitement of the vegetative nerves. Regular and very manifold is the involvement of the other glands of internal secretion which, for the most part, is secondary. The syndrome that results depends, therefore, not upon the degree of

hyperfunction, but on the constitution of the individual affected; that is, on the reaction capability of the ductless glandular apparatus. The cause of hyperthyrosis is not at present known. The possibility exists that it is conditioned centrally and that many symptoms of Basedow's are coördinate with the hyperthyrosis."

Etiology

Hereditary disposition appears to be traceable in a fair number of cases. By far the greater number of cases occur in females, a ratio estimated as high as ten to one. The usual age is from 16 to 40. Falta says the goitre noxus plays only a subordinate rôle. Emotional causes, fright, long continued anxiety, etc., are generally held to be factors in etiology, but it is probably true that, to be effective in causing the condition, they must be superimposed upon a neuropathic predisposition. Acute infections are noted as preceding many cases, and rheumatic fever, typhoid fever, influenza, malaria and others have all been regarded as of some significance. Focal infection may be a factor. In the study of 50 consecutive cases by Kessel, Hyman and Lande, they found:

> "By far the most frequent and important exciting causes were psychic insult. In 72% of the histories, this was in immediate relationship to the onset of the disease. Focal infection played an exciting rôle in 40%, the focus being present almost constantly in either the tonsils or the sinuses. Alteration in sex life and dietary insufficiency were active in a small number. In many of the patients more than one exciting factor occurred."[22]

The long continued use of iodine compounds or thyroid preparations may be causative, although it is stated that in a very large series of cases of administration of iodine to prevent or cure simple goitre not a single case of Basedow's developed. The cause or causes of Basedow's are unknown so far as any positive knowledge of their relationship to the mechanism at work in instituting the condition is concerned.

Pathogenesis

One of the views commonly held postulates a nervous origin of the condition. Injury to certain areas in the brain (medulla) is known to produce tachycardia, exophthalmus and thyroid vascular enlargement and many symptoms of Basedow's are similar to those produced in this manner. But it is not possible to thus produce a condition of experimental exophthalmic goitre. Moreover, pathological findings corroborative of such a theory are rare, although it is possible that there may be a functional phenomenon arising in the medulla and accounting for the origin of exophthalmic goitre. Holding much greater interest, however, than origin in the central nervous system is the relation of the vegetative nervous system. The emphasis of Falta in this connection is embodied in his definition (see above). Many believe that if not causative the affection of the vegetative nervous system is inseparably bound up in the exophthalmic goitre process—antecedent, concurrent or consequent. In a résumé of their studies on the subject, Kessel, Hyman and Lande[22] conclude that:

"1. Thyroid hyperplasia and thyroid adenoma may exist for years without at any time causing sympathomimetic symptoms or alteration in metabolism.

"2. Disturbances of the involuntary nervous system clinically occur frequently (autonomic imbalance).

"3. Such disturbances are usually not attended by metabolic elevation.

"4. While these clinical manifestations of disturbances of the involuntary nervous system (autonomic imbalance) are often associated with thyroid hyperplasia, there is no reason to believe that the thyroid enlargement is causative and many reasons for thinking that it is secondary and symptomatic.

"5. In exophthalmic goitre the dominant derangement is in the realm of the involuntary nervous system. This may not be primary, but the primary cause, whatever it be, must at least operate through the medium of the involuntary nervous system.

"6. The primary cause of goitre must be sympathomimetic.

"7. There is a close relationship between exophthalmic goitre and autonomic imbalance. The latter usually presages the former and is probably a stage of its development."

The theory here is to regard exophthalmic goitre as arising from a diathesis which is in this case autonomic imbalance. This is probably an inherent mode of reaction of the particular organism, and a "cure" from Basedow's in such a case would not restore the individual to normal but simply to the original condition of autonomic imbalance.

The work of Wilson,[24] in the experimental production of exophthalmic goitre in goats, is suggestive of the vegetative nervous system as a central factor. He found that "the injection of freshly isolated virulent cultures of *bacillus bronchisepticus* into the superior cervical sympathetic ganglion of adult goats usually produced marked constitutional symptoms, such as trembling, increase of temperature and loss of appetite, and frequently caused death in from three days to three weeks. No exophthalmus was noted." The histological appearance in the thyroid of the goats resembled that found in early exophthalmic goitre. It is concluded that "this evidence supports the suggestion that in exophthalmic goitre the thyroid receives its stimulus to overfunction through its nerve supply, and as a result usually of a local infection in the cervical sympathetic ganglia."

Theory of Thyroid Origin

As has been stated above, many hold the theory that exophthalmic goitre is due simply to an increased thyroid secretion—the theory of Moebius. Many facts support the theory and the objections to it have been stated. The theory of faulty, toxic secretion—dysthyroidism—has also been discussed.

Theory of Infection and Intestinal Toxemia

This has been held by a number of workers, the chief of whom is perhaps McCarrison. In his work in Northern India, both clinical and experimental, he has collected much evidence in favor of this theory of goitre in general. He states: "This accumulation of facts demonstrates, I believe, that the causal agents of goitre, as well as of

its congenital manifestations, are micro-organisms, inhabiting the alimentary tract of sufferers from this disease, and often of other persons whose thyroids show no actual enlargement, but which nevertheless may be in a hyperplastic state. Except in so far that all the epidemiological and experimental facts point to anaerobic organisms as the causal agents of this disease, they do not permit of a more definite conclusion as to the identity of these organisms."[25] While there would seem to be little doubt that such agents may act in producing goitre, or even exophthalmic goitre, it certainly does not appear that they can be regarded as the sole cause of either. (See McCarrison's statement under "Etiology of Goitre.")

In considering exophthalmic goitre and its pathogenesis, it would appear that there may be elements of all three theories, and particularly of the neurogenic and thyrogenic, which are at work. It seems quite certain that much of the symptomatology arises through the action of the vegetative nervous system, and it is also probable that the thyroid activity—either excessive or perverted—is stimulated by the activity of the vegetative system. Whether the stimulus to activity of the vegetative system lies more remotely in the central nervous system in some areas of the brain is not certain. The surprising frequency with which emotional and psychic disturbance precedes the condition might point to this. The ideas of Falta, as to individual susceptibility to the various internal secretions, are also to be considered. Falta believes that individuals vary greatly in their reactions to such stimuli and that varying syndromes or no reaction at all may result in different individuals in response to the same stimulus. He says:

> "The greater intensity of the symptoms in true Basedow's always admits of the possibility that hyperthyroidism is only a partial phenomenon of an alteration of the central nervous system and that the organism of the Basedow's patient reacts to a hyperthyroidism in a different manner than the normal. The foundation for this can perhaps be seen in a constitutional alteration of which the cause lies in the associated involvement and perhaps in a functional increase of other ductless glands. The final cause of all the manifestation may well be regarded as lying in the central nervous system."

Symptoms, Physical Signs, Diagnosis and Pathology

The cardinal symptoms are exophthalmos, goitre, palpitation of the heart and tremor. The nervous apprehension and appearance of alarm is characteristic. In the study by Kessel, Hyman and Lande, the following were found: "Asthenia (88%), loss of weight (84%), palpitation (84%), nervousness (80%), were the most frequent symptoms. Of the cardinal symptoms of exophthalmic goitre, goitre was present in 78%, and the subjective presence of exophthalmos was reported in but 60% and of tremor in 70%. The surprising frequency of dyspnea (62%), vomiting (30%), dysphonia (24%), dysphagia (10%), headache (28%), precordial pain (14%) and pain in the eye (16%), is worthy of comment." Goetsch[26] also

finds asthenia of great diagnostic value, and states he has come to look upon it as a more important feature than even nervousness. Hertzler also mentions muscular fatigue as a constant accompaniment.

Christie [27] places the following relative value on the various signs: (1) Positive anamnesis; (2) Uniform dilatation of the heart with rapid rate, provided other factors which might cause these heart signs have been eliminated; (3) Increased basal metabolism established by careful and repeated measurements; (4) Presence of signs directly referable to the thyroid gland; (5) Presence of characteristic eye signs; (6) Tremor, sweating hands and pigmented skin.

Increased Basal Metabolism

The basal metabolism is raised in marked degree—the increase of oxygen consumption amounting in some cases to almost 70%. In 182 cases of exophthalmic goitre studied by Sandiford, there was an average metabolic rate of plus 51% before treatment.[28] The whole physiological process gives evidence of the increased oxidations of the body. In fact, this is one of the points in favor of a hyperthyroid theory of pathogenesis. The protein metabolism is first affected and there is increased nitrogen in the urine and demand for protein food. The fat and carbohydrate metabolism are increased but less directly. Sanger and Hun [29] find, in a study based on ten normal controls and ten well-marked cases of exophthalmic goitre, that the carbohydrate metabolism constantly increased in Basedow's, with the respiratory quotient showing a rapid rise, indicating an actual increase in carbohydrate metabolism.

> "It has been shown that in hyperthyroidism, sugar, when it is offered to the tissues as a fuel, is burned with great avidity. The increased utilization of carbohydrate, after carbohydrate ingestion, along with the maintained high blood sugar, points to an inability to store glucose, most probably a failure of liver storage, due to some toxic change in the liver caused by the disease. This fits in with the results found in thyroid fed animals, and is suggested by clinical cases of exophthalmic goitre in which carbohydrate restriction is attempted."

Boothby and Sandiford [30] conclude, from a study of the material at the Mayo clinic, that there is no measurable increase in the endogenous protein metabolism in Basedow's and that it cannot, therefore, be the cause of the increased basal metabolism.

> "The cells consume at an accelerated rate whatever type of food is brought them, but in none of our experiments is there any evidence to indicate that any of the three food substances, fat, carbohydrate or protein, is burned in a qualitatively abnormal manner. As in the normal subject, the body's own stores of these substances are not drawn on except to meet deficiencies in food intake."

The hyperglycemia of Basedow's is usually stressed and glycosuria is also found, and it is usually held that the assimilation limits for carbohydrates are lowered. The work, therefore, of Sanger and Hun, showing actual increase of sugar oxidation and continued hyperglycemia, is very

suggestive, as well as the supposition that the defect lies in sugar storage in the liver. This supposition finds support in the study of Kuriyama,[31] who found the feeding of thyroid distinctly decreased the glycogen content of the liver in experimental animals.

Diabetes and hyperthyroidism may occur at the same time in some cases, but there is no evidence of any causal relationship between the two.[32] The carbohydrate metabolism of Basedow's is but little understood and the disturbances are of such a variety as to make them impossible of explanation by any known theory. The increased metabolic rate is of great importance in establishing a diagnosis of true Basedow's and some observers[33] make it the deciding point in diagnosis:

> "We have arbitrarily chosen to accept the basal metabolism as the best available objective diagnostic sign. For the present we do not accept as exophthalmic goitre a case in which there is not, or has not been, a constant and distinct elevation of the basal metabolism."

It should be noted, however, that one of the peculiarities of the disease is the occurrence of periods of hypothyroidism following hyperthyroidism, or even hypothyroid symptoms occurring at the same time. This may point to great instability of the thyroid, but it could be well explained on a basis of dysthyroidism.

Diagnostic Eye Signs

A number of signs referable to the eye are of value in diagnosis; the principal ones are:

1. The exophthalmos itself, the characteristic protrusion of the ball of the eye giving rise to the peculiar staring expression, occurs in all degrees or may be absent. The eyeball is apparently actually increased in size. The protrusion, however, is said to be (Falta) due to abnormal tonus of the Landström musculus palpebralis through its innervation by the sympathetic and by others of Müller's muscle. (This explanation is denied by Murray: British Medical Journal, Nov. 11, 1922.)
2. Dalrymple—Stellwag sign—The widening of the palpebral fissure.
3. Stellwag's sign—A condition of suppressed involuntary winking.
4. von Graefe's sign—Failure of the upper lid to follow the eyeball down, in looking downward, due to increased tonus of the levator palpebral muscle.
5. Moebius' sign—Weakness in convergence of the eyes. On fixing the eyes on a finger one eye will turn to the outside, particularly when the finger is brought close to the eyes.
6. Loewi's test—In pancreatectomized animals, in diabetes and in hyperthyroidism, instillation of 1-1000 solution of epinephrin produces dilatation of the pupil.

Special Tests

Kottman Reaction for Thyroid Activity. This serum test for thyroid activity is based upon the principle of colloid chemistry relating to "protective colloids." Roughly this may be described as the property which some colloidal substances have of so influencing others as to render them capable of remaining in colloidal

solution—whereas alone they would precipitate. Kottman assumes that excess thyroid secretion in the serum raises this protective capacity over normal or hypo-normal serum. Therefore, silver iodid will be in finer suspension in hyperthyroid serum than in normal or hypothyroid serum, and as fine particles of silver iodid are less sensitive to light than coarser particles the addition of a substance such as hydrochinon, which acts as a developer, will give different results to different sera.

> " Technic—The technic of the reaction is simple and depends on the protective property of the serum for silver iodid. When the protective power is great, the size of the silver iodid particles dispersed in the serum remains small and the photosensitivity of the silver iodid is reduced. If the protective power of the serum is poor, the silver iodid forms larger particles, becomes more photosensitive, and will, on exposure to light and subsequent development, be readily reduced to metallic silver.
>
> " To 1 c. c. of clear serum, obtained preferably in the morning before meals, 0.25 c. c. of 0.5% solution of potassium iodid is added and 0.3 c. c. of a 0.5% solution of silver nitrate. The reagents should be prepared freshly and accurately measured. After mixing by gently agitating the tube, the serum is exposed for five minutes at a distance of 25 cm. to a 500 watt mazda lamp. Then 0.5 c. c. of a 0.25% solution of hydrochinon is added, and the color changes noted at definite time intervals. Readings can be made on a 4 plus basis, or colorimetrically against some arbitrary color standard. In some of our work we have used a solution of dialyzed iron for this purpose and readings are then expressed in terms of a color unit. Serum from cases of hyperthyroidism retards the development of the brown color; normal serum turns brown within a short period of time; serum from cases of hypothyroidism accelerates the appearance of the dark brown color." [34]

This reaction in the hands of a not great number of observers who have used it has proved specific to a surprising degree and the number of conditions which, other than hyperthyroidism, will produce it is apparently small.

Goetsch Test. This test for hyperthyroidism is of value in diagnosing borderline cases.

> " In 85% of the cases the Goetsch tests are in agreement with the metabolism estimation. (Basal metabolism estimations themselves are distinctly less than 100% accurate.) " [35]

The test is performed as follows: Six or seven minims of a 1-1000 solution of epinephrin are injected subcutaneously and the effect on the blood pressure, pulse and respiration and the general reaction is noted. In a positive reaction there is an increased blood pressure of from 10 to 50 or more mm. The average is from 15 to 20. Among the general symptoms noted in a positive reaction are symptoms of general unrest and nervous excitement, tremor and disturbances of capillary circulation of the skin. The test should ordinarily not be given in cases of high blood pressure or

severe Basedow's. The patient's subjective symptoms should be elicited and help in the diagnosis. If the patient is not calm to begin with, the test may be delayed. It should be added that numerous investigators have questioned the specificity of the Goetsch test and its value in diagnosis. It is, however, very probably a procedure of value in doubtful cases.

Involvement of Other Glands

Other organs of internal secretion are involved with more or less constancy, and may modify the usual picture; but there is nothing constant or characteristic about such changes, although there have been numerous writers who have held a pluriglandular origin of this condition. Although there is almost no doubt that other organs of internal secretion usually show abnormalities in exophthalmic goitre, there are no well-defined changes constantly occurring and certainly none which would justify assuming that these associated changes are etiologic. The suprarenals are frequently involved and symptoms of suprarenal insufficiency may be present. The pituitary may, and frequently does, account for many of the symptoms in well-developed Basedow's. The thymus has always been a subject of interest in this relation, and it is generally believed that it is most constantly involved. Autopsy findings show a surprising percentage of thymus involvement (some reporting as high as 100%). The usual changes are hyperplasia and hypertrophy. The blood shows changes, and although there is as a rule no marked affection of the erythrocytes the lymphocytes are largely increased, and there is an appreciable increase in the mononuclear cells.

Hyperthyroidism (simple) may frequently bear a close resemblance to such states as neurasthenia, and for the differential diagnosis reliance must be placed upon a careful analysis of all elements in the syndrome. "Hyperthyroidism cannot be differentiated from neurasthenic states, nor heart disease from these neurasthenic states, by any special laboratory method."[36]

Treatment

Surgical treatment may frequently be necessary, although the results are far from certain or satisfactory. Statistics as to the results obtained vary, but there is certainly not enough promise to make surgery a method of choice, although it has been advocated by several writers (surgeons). The arguments against surgery are well set forth by Bram.[37]

X-ray has many advocates and in the hands of experts and in institutions may give good results. The results in the Massachusetts General Hospital[38] showed that almost two-thirds of the genuine Basedow's showed either recovery or improvement under irradiation with x-rays. Medical treatment is ineffective in many cases, and there is little general agreement as to what should be included in treatment. Bram says: "Strict individualization of the case in hand is the dominating principle of treatment. The proper medical attendant, the proper social atmosphere and the right kind of dietetic, hygienic, medicinal, psycho-therapeutic, electro-therapeutic and other measures properly applied for the required length of time should yield permanent cure." Before any other measures in medical treatment are attempted there should be a thorough search for any foci of

infection in the body, pyorrhea alveolaris, septic tonsils, chronic appendicitis, septic gall-bladder, etc. Free catharsis should be established and throughout treatment the bowels should be kept in a normal, healthy condition.

The establishment of an atmosphere of calmness, repose and freedom from excitement and disturbance is indispensable. For this reason, selection of an attendant is of the greatest importance. Failing to attain the proper quiet by ordinary means, actual isolation in a quiet country place or at home and retirement from business and domestic cares and worries may be necessary. Rest and absence from physical exertion are essential. The habits of life should be simple and systematized. The cultivation of pleasant associations in the open air is desirable and moderate exercise in the open may be helpful. Electrotherapy and hydrotherapy are frequently of definite value. The diet should be ample and mixed. The necessity for a diet of sufficient calories is important. The calory requirement in Basedow's is high and to remain in balance the diet must be adequate. Boothby and Sandiford [39] have pointed out that, unless the calory requirement is supplied by the diet, there results a weakened condition, loss of weight and decreased resistance.

Quinine has been advocated, and Bram states: "Especially in the form of the neutral hydrobromate or hydrobromide quinine is the drug par excellence in the treatment of exophthalmic goitre." Arsenic and arsenic and mercury have been recommended. Thymol as an intestinal antiseptic is used by McCarrison, who also has found the neutral hydrobromide of quinine "administered in five grain doses thrice daily has appeared to me to justify the enthusiasm of some authors for it." [40] Watson [41] has found injection of from 1 to 4 mils. of a 30 to 50% quinine and urea solution per day useful. He repeats the injection about every third day. Eight to fifteen are usually necessary to bring improvement. Mendel [42] finds iodine and arsenic of value, and states that the results are prompt and have never failed absolutely. He used intravenous injections of a solution of atoxyl and sodium iodid in water.

Belladonna and atropine should be used cautiously if at all, as they depress the vagus and would aggravate the symptoms described by Eppinger and Hess as "Sympatheticotonic." Bram states that ichthyol has proved of brilliant service. He says, "In combination with quinine it becomes a very powerful formula controlling the cardinal symptoms more promptly than anything I have ever used." He gives the following prescription:

Quinine Hydrobromide	gr. 5.
Arsenii Trioxidi	gr. 1/40.
Ichthyoli	gr. 1.

In capsule after meals and at bedtime.

For the control of the nervous irritability and restlessness, bromides, veronal, etc., may be used. Daily evacuation of the bowels should be secured. For the palpitation of the heart, an ice bag over the heart or thyroid region should be used in combination with absolute rest.

The teaching has been against giving iodine in any form in exophthalmic goitre, on the theory that it increases the presumed excess thyroid secretion. However Bram states, "Personally, I feel that iodine may be

tried with impunity in exophthalmic goitre, if results are carefully noted." As the underlying cause may be lack of iodine, its administration may be useful. Kendall (quoted by Bram) states: [45]

> "The relation between iodine and clinical symptoms is very difficult to explain, but it seems probable that the determination of the functioning groups in the active constituent of the thyroid will throw much light on the subject. It is possible to explain the toxic symptoms produced by the hyperplastic thyroid by assuming that an excess of its secretion is being formed. This can be disproved by the fact that the amount of iodine in the gland is lower than normal, which probably is not entirely explained by the immediate pouring out of the substance from the gland, although this may, in part, be the explanation. Another explanation is that the gland produces thyroxin without the iodine attached. The body would thus be supplied with possibly an enormous quantity of the functioning part of thyroxin, which could theoretically produce the effects that are known."

Plummer [44] also states that in Basedow's the normal thyroxin may not be completely iodized and this imperfect thyroxin can enter into catabolic reaction faster than the normal, stable molecule and raise the metabolic rate more rapidly. Hence, if it is possible to change the character of the molecule it would be possible to change the metabolic rate. The administration of small amounts of iodine (10 drops of compound solution for 10 days) entirely eliminated postoperative deaths from hyperthyroidism. "In other words, the patient is relatively short of iodine and dies from lack of it. When we replace the iodine we do away with postoperative deaths." For the general practitioner, however, it is undoubtedly safer to avoid iodine in the treatment of Basedow's.

Organotherapy Among the organotherapeutic substances used for special or general treatment are parathyroid, pituitary, thymus, suprarenal, ovary and pancreas. Parathyroid is indicated in those cases giving symptoms of parathyroid insufficiency. T. B. Scott,[46] in discussing treatment, says: "Parathyroid always, in addition to anything else one may be giving. Full doses are needed: ¼ gr. of the dried extract three times a day is generally sufficient, but this dose may be increased." Pituitary extract has many advocates, and the experience of Solis-Cohen in one case reported was most favorable. Pancreas therapy is undoubtedly useful in many cases and may act through its antagonistic action on hyperthyroidism. Suprarenal substance has been successfully used and by some is stated to be the most effective substance used in organotherapy. In a report of a case, Shapiro and Marine [40] found the oral administration of suprarenal cortex effected very rapid and striking improvement. Rogers [47] reports three cases treated with adrenal preparations, with very favorable influence on the symptoms, and with his associates reports [48] the effects upon the increase of iodine content in the thyroid of dogs. With various adrenal products, fed by mouth, they increased the iodine content in amounts varying from 50.7% to 70.4%. Epinephrin gave no increase at all in increasing the thyroid iodine, so that they conclude, "An extract of the entire gland

containing something more than pure epinephrin has thus been demonstrated to have a direct effect upon the thyroid gland."

In the treatment of these cases the hygienic treatment and rest are all important. Kessel, Hyman and Lande state that the spontaneous course of exophthalmic goitre is toward arrest in the great majority of cases. If cases developing the disease between 45 and 50 be excepted, "The prognosis is excellent under a regimen of skillful neglect." A similar opinion is held by Stanton:[49] "My studies of the prognosis of exophthalmic goitre have led me very firmly to the belief that there are only two major factors in the non-operative treatment of exophthalmic goitre—rest and time. Drugs and various other measures may tend to give some degrees of temporary subjective relief, but there is no proof in any of the articles so far published that the improvement noted is anything other than that to be expected in the natural course of the disease."

With reference to the relative advantages of medical and surgical treatment, Stanton says: "After five or six years there is probably little to choose from between the medical and surgical in the results, as regards either the mortality or the condition of the surviving patient."

GOITRE

Bronchocele, Struma

> "A chronic enlargement of the thyroid gland not due to a neoplasm, occurring endemically in certain localities, especially mountainous regions, and sporadically elsewhere."[52]

Goitre as here discussed refers to a simple chronic hypertrophy and hyperplasia of the thyroid gland. It occurs as an endemic disease in some localities and sporadically in practically all parts of the world. In a goitre district in Michigan, Levin[52] examined 1783 unselected persons, ranging in age from newborn to 61 years and including 790 males and 993 females. He found in this group 682 simple goitres (without symptoms), 230 males and 452 females; 420 adenomatous goitres, 119 males and 301 females; and 44 colloid goitres, 6 males and 38 females. It is interesting to note that in such a district Basedow's was found in relatively small numbers, cretins are rare and hypothyroidism not common. In a goitre survey among school children in Grand Rapids, Michigan, among 26,215 pupils 30% had enlarged thyroids; 32% of these were boys and 67% girls. The life history of goitre in the male and female is shown in Levin's study. The percentage of goitre rises rapidly in both male and female as puberty is approached, but it is higher in the female than in the male. In the female, in the period from 10 to 15 years, the percentage is about 94, while for that period the male average is about 68. In the female, however, the percentage is maintained above 80 following puberty, but in the male it drops to about 20 between 35 and 40 years, rising to 32% at 42 and receding to 20% in later life.

Goitre is the expression of an effort on the part of the thyroid to maintain a normal quantum of thyroid hormone and may result from localized trauma or injury of any kind, nervous, toxic or chemic, which

impairs the functional activity of the gland in the production of its hormone. It may, therefore, be associated as a part of general hypothyroidism, or it may occur in Basedow's disease, or as part of a general systemic disturbance resulting in stimulation of the thyroid with resulting excess reaction beyond the requirements of the body or to meet unusual and added requirements. The first changes in goitre are probably hyperplastic, in which the epithelium proliferates to meet the needs of a hypothyroid condition, or a deficiency of iodine, or to compensate for an imperfectly formed secretion. When a normal condition and normal requirements are again established, there is a reversion to the colloid type. In dysthyroidism, although the output (postulated) of toxic iodo products is large, there is a hypothyroidism nevertheless (lack of normal thyroid hormone) and the defective gland hypertrophies to meet the requirements of the body. General increased demands of the body for more thyroid hormone, such as occur in pregnancy, may result in physiological hypertrophy, which if it persists after the need has passed results in a goitre. This type of goitre is sometimes classed as a "simple goitre" and is differentiated from colloid goitre by some authors. As there seems to be an exceedingly thin line of demarcation between the two in this description, they will be described under the single heading "simple colloid goitre." "Simple" goitre, if described as a separate class of goitres, is the simple hyperplasia which occurs at puberty and at times during menstruation and at pregnancy. It is simple enlargement, usually not permanent, without symptoms.

Etiology

The etiology of simple goitre is almost no better known than that of Basedow's. Many factors are known to be active in producing it, toxic agents, focal infection, lack of iodine, intestinal toxemia, etc. All may be sufficient to cause goitre. The relation of iodine deficiency is discussed under Prophylaxis. McCarrison,[4] who has been active in bringing attention to the intestinal factors, states that this is not in discord with the work on iodine deficiency. He points out that, although iodine may be lacking in the food supply, goitre commonly occurs when the iodine is present in sufficient amounts, and points out one experiment to prove this. If animals are confined in dirty cages, they will develop goitre spontaneously. If, however, they be confined to scrupulously clean cages of the same dimensions, goitre does not arise. Since the food supply and iodine content were the same, the experiment shows that the unhygienic conditions in some way render the iodine of the food unavailable and insufficient for the needs of the body. "While, therefore, simple goitre is due theoretically to insufficiency of iodine, it is due in practice to a combination of factors, which together bring about this insufficiency." It is evident from McCarrison's work that the two great current theories as to causation of goitre may be part of the same process.

Classification of goitre has never been wholly satisfactory. There is in the literature a diversity of nomenclature, so that the reader is frequently confused as to what particular pathological and clinical condition is referred to. One of the most comprehensive, as well as simple, classifications appears

to be that of Hertzler.[55] Under this classification practically all goitres may be classified, and as clinical types are related to pathological findings, it permits of a general understanding of the many types described in the literature and named under the most varied systems of nomenclature. Various combinations of these groups may be encountered. These group types are:

1. Colloid goitre.
2. Adenomatous goitre.
3. Interstitial goitre.
4. Degenerative goitre.

Colloid Goitre This is the simple, non-toxic type of goitre, which may persist for years without symptoms. "The only symptoms presented by colloid goitre are those due to the resultant compression of the surrounding structures."[56] These goitres may become very large and hang in a great mass, which may be median, or to either side, depending upon the lobes involved. It is the type commonly found in endemic goitre. Microscopically, the alveoli appear distended with colloid, and the alveolar epithelium is not notably altered. Graham[57] states, "The chief differences between a normal gland and a colloid goitre are the following: The colloid goitre has been hypertrophic or hyperplastic or both, and has recovered; it is usually larger than the normal gland; the follicles show greater variation in size and shape; the lining cells are more apt to be flattened; the stroma is increased." The changes may not involve all parts of the thyroid or all acini, but may occur here and there through the gland. After these goitres have developed, become stationary or resting and old, they may and frequently do undergo changes, such as calcareous deposits, cystic degeneration and degenerative changes. The cysts are usually filled with colloid and the cyst cavity is really a space made up of several broken down acini. The cyst may contain blood and on cut section numerous bloody cysts may be found. Deposits of calcareous matter, even in considerable quantity, may be encountered and malignant changes may occur in 1% of all goitre cases, according to Williams.[58] The complication of principal interest, however, is the development of degenerative or proliferative changes in the pre-existing colloid goitre. These changes result in the Secondary Toxic Goitre of Hertzler's classification (degenerative toxic goitre). The toxic symptoms develop after years of no symptoms in a benign colloid goitre. The age of onset is usually in later life. Symptoms of nervousness arise and the patient exhibits all symptoms of toxic goitre. The colloid shows most of the changes, is retracted from the cell, shows altered staining characteristics and may be filled with cells from the acinar wall.

Adenomatous Goitre The adenomatous goitre is characterized pathologically by the adenoma-like proliferation of the parenchyma cells, and clinically by the resulting hyper—or dysfunction—the marked thyrotoxicosis. These goitres may be divided on a pathologic basis into *fetal adenomatous goitre* and *diffuse adenomatous goitre*.

The fetal adenoma is localized in definite capsule formation and may not be toxic. The colloid is reduced or absent, but may be present when

toxic symptoms arise. The increased number of acini accounts for the growth. The structure has then the appearance of the gland in the fetus. The goitre may be limited to these encapsulated masses or include a general adenomatous condition of the whole thyroid.

Diffuse Adenomatous Goitre

1. Glandular Type: The essential pathologic picture here is in the acinar epithelium which undergoes proliferation and becomes overactive. New acini may also develop from the increased activity of the epithelial cells in the interstitial tissue.

2. Papillary Adenomatous Goitre: Here there is a proliferation of the acinar epithelium resulting in projections or papillæ into the acini. This type of pathology is "distinctly associated with exophthalmic goitre" (Hertzler). The new formed papillæ may be present in enormous number and the overactivity is very great. Colloid may be absent, or, if present, show degenerative change. Clinically the thyrotoxicosis is the prominent symptom. The degenerative changes may finally overshadow the proliferative and as this becomes marked they resemble the secondary degenerated cases with secondary degeneration.

Interstitial Proliferative Goitre (Forme Fruste)

In this type of goitre the pathologic changes are exhibited by the interstitial epithelial cells. The colloid and the acinar epithelium are but little affected. The interstitial proliferation may result in the formation of new acini, which contain colloid. There is no great difference in appearance of these proliferated interstitial cells from the cells of the acini.

Degenerative Goitre

Secondary adenomatous, proliferative toxic goitre. This type of goitre develops in old colloid goitres which have remained without symptoms for many years. All the secondary changes found in such goitres may be present. "Instead of there being a degeneration of cells, there is usually somewhere in the gland a rejuvenescence of the cells." All the symptoms of toxic goitre, and even the eye symptoms, may be present; the metabolic changes are less developed. There may be more or less round cell infiltration of the connective tissue. The colloid shows changes such as vacuole formation and contains epithelial cells detached from the acinar wall.

Relation of Pathology to Symptoms

The statistics collected by Williams,[59] in a study of 100 cases of goitre, are interesting in the light they throw upon the relation of the symptoms of goitre to the various pathologic types of goitre. Williams divides his cases into three groups as follows:

I. Simple goitre, with few symptoms other than those due to pressure.

II. Is composed of cases in middle age, in which goitre has been present for a long time without symptoms and suddenly begins to grow, with the development of restlessness, nervousness, attacks of palpitation and acceleration of the heart and loss of weight. They do not have exophthalmos or fine tremor.

III. "Embraces the patients with classic symptoms of exophthalmic goitre: they present a line of symptoms, including all in group II, but in addition definite points which put them in a separate class."

The following data, especially the pathologic findings taken in relation to the composite case histories, may be considered with the classification given above.

It will be noted that simple colloid goitre furnishes the largest single item in group I (without symptoms), and that cystic degeneration of the colloid type with simple and fetal adenomatous goitres practically completes the group.

In group II (with toxic symptoms) colloid goitre with parenchymatous hyperplasia forms the largest single item, and fetal adenoma and simple colloid goitre practically complete the group.

In group III (Basedow's) severe papillary hyperplastic parenchymatous goitre practically makes up the group.

It will be noted that there is fair agreement and uniformity in the relation of pathologic types to resulting symptoms.

Simple colloid goitres tend toward freedom from symptoms, although they may (in about 25% of the cases) give rise to toxic symptoms (perhaps always through secondary changes).

Simple adenomatous goitre tends strongly to freedom from symptoms.

Fetal adenoma tends to freedom from symptoms, but they may be present (in about 33% of the cases).

Colloid goitre with parenchymatous hyperplasia is almost always attended by symptoms.

Papillary hyperplastic parenchymatous goitre is characteristically found in Basedow's.

The composite case reports, together with the pathologic findings, follow:[88]

> "Group I contains the simple goitre, about which there is little to be said. They have few symptoms occasionally complaining of pressure, as evidenced by hoarseness, obstruction to breathing and difficult swallowing. They come to operation for relief of these symptoms, or, as is more frequent, for a correction of the deformity.
>
> A summary of the cases in this group is as follows:
>
> Number: 61.
>
> Sex: Males, 4; females, 57.
>
> Age: Twelve to sixty years. Average, thirty-two and a half years.
>
> Duration: Two months to twenty-five years. Average, seven and a half years.
>
> Growth: Gradual increase in size in all cases except three, these of twenty-five, ten and five years duration had grown more rapidly in the year preceding operation. The pathologic report in all three cases was cystic colloid goitre.
>
> Tachycardia: One case.
>
> Tremor: The fine fibrillary tremor was absent in all cases. A few had a gross tremor. Loss of weight was noted in only two cases.

Nervousness: Thirty-six per cent of the cases were nervous but none were of the toxic type of nervousness.

Recurrence: Two cases were recurrent. The pathologic reports were cystic and cystic colloid goitre.

PATHOLOGIC REPORT

Simple adenoma	12
Colloid goitre	24
Cystic goitre	10
Fetal adenoma	10
Hematoma	1
Colloid with parenchymatous hyperplasia	1
Adenoma with parenchymatous hyperplasia	1
No report	2
Total	61"

"Group II. A summary of the cases in this group is as follows:

Number: 20.

Sex: Male, 1; females, 19.

Age: Thirty-four to fifty-eight years. Average, forty-seven years.

Duration: Two months to thirty years. Average, eleven years.

Growth: Recent growth of goitre in 10 of 14 cases recorded, 77%.

Tachycardia: Present in 35%.

Exophthalmos: Absent in all cases.

Tremor: The fine fibrillary tremor was absent in all cases. Gross tremor in 35%.

Loss of Weight: 5 to 100 pounds in 40%.

Nervousness: All these patients complained of being nervous. In one case, the only postoperative death, it amounted to a dementia.

PATHOLOGIC REPORT

Colloid with parenchymatous hyperplasia	7
Fetal adenoma	3
Colloid	6
Simple adenoma	1
Cystic	1
Fetal adenoma with parenchymatous hyperplasia	1
No report	1
Total	20"

"Group III. A summary of the cases in this group is as follows:

Number: 19.

Sex: All females.

Age: Fifteen to fifty-one years. Average, thirty-three years.

Duration: Two months to seven years. Average, two years.

Growth: Recent growth of goitre in 8 of 14 cases recorded, 57%.

Tachycardia: Present in 86%.

Exophthalmos: Present in 60%.

Tremor: The fine fibrillary tremor present in 86%.

Loss of Weight: Ten to forty pounds in 30%.

Nervous: All were typically nervous, as evidenced by rapid speech, movement of limbs, excitability, etc.

PATHOLOGIC REPORT

Severe papillary hyperplastic parenchymatous	14
Simple adenoma with parenchymatous hyperplasia	1
Colloid with parenchymatous hyperplasia	1
No report	3
Total	19"

PREVENTION OF GOITRE

Through the researches of Marine and Lenhart and of Kimball and Marine, it has been demonstrated that goitre may be effectively prevented by the administration of some form of iodine. They have shown that in goitres the iodine content is reduced, and if the amount contained in the thyroid falls below one-tenth of 1% hypertrophy and hyperplasia begin and goitre results, and that this deficiency may be made up by the administration of iodine compounds. The efficiency of this procedure was not only proven in animal experiments and observations on sheep and on fish, but was given practical trial on a large scale in a goitre district among school children. The striking effects of the iodine administration are evidenced by the following:

> "Of those that were normal at the first examination and did not take iodine, 347 or 27.6% had enlarged thyroids, while of those that were normal at the first examination and took iodine as outlined, 2 or 0.2% had enlarged thyroids. * * * Of the cases classed as having slightly enlarged thyroids at the first examination and not taking the prescribed iodine, 127 or 13.3% underwent further enlargement, while among those taking the prescribed treatment only 3 or 0.3% underwent further enlargement. * * * Of the 2305 cases not taking iodine, 495 showed thyroid enlargement. Of the group with small goitres taking iodine, 659 or 57.8% returned to normal, while of the same group not taking iodine at school, 134 or 13.9% returned to normal."[61]

Some of the latter, however, received iodine at home under the direction of their physicians. The iodine was administered as sodium iodide in a daily dosage of 0.2 gm. until 2 gms. were given and repeated each spring and autumn. There were no ill effects noticeable other than a mild rash in an insignificant number.

Treatment

In cases of simple goitre, without toxic symptoms, the results of iodine therapy are usually good. The matter of the preceding paragraphs bears on this point. This includes the adolescent goitres. Thyroid extract (beginning with 1/10 grain t. i. d. cautiously increased) may be equally effective, but is perhaps more dangerous and requires very careful supervision. Iodine may be given as sodium iodide 0.2 gm. daily until 2 gms. are given; or as syrup of the iodide of iron in five-drop doses three times daily.

Toxic symptoms developing in the course of treatment are always signs for discontinuance and caution. Colloid goitre may respond well to treatment by iodine. Focal infection, infected tonsils, etc., should be carefully sought for, and the gastrointestinal tract should be maintained in a healthy condition. Good hygiene and a suitable diet are important. The diet should be low protein and not devised to cause intestinal putrefaction.

Surgery should not be delayed too long if medical treatment is unavailing or if there is evidence of degenerative toxic change.

As a general guide to treatment, basal metabolism is perhaps the best index of treatment.

> "The importance of basal metabolism studies in the handling of thyroid diseases must be recognized. By metabolic rate determinations we are greatly aided in our diagnosis of early and obscure cases of hyperthyroidism. Moreover, the degree of severity of an obvious hyperthyroidism can be determined by this test. Again the presence or absence of toxicity of an adenomatous thyroid is made evident through these metabolic studies. As a guide for surgical removal of goitres, surgeons are recognizing the value of this test. Finally in the diagnosis of hypothyroidism and in directing and gauging thyroid administration metabolic rate determinations are of the greatest importance." [62]

Thyroiditis—Inflammation of Thyroid

Inflammation of the thyroid tissue may follow acute infection or occur during the course of chronic infections, such as tuberculosis and syphilis. These conditions are not common. In acute virulent infective processes the onset may be sudden and the local symptoms of pain and pressure severe. Pus formation may occur. It is probable that diagnoses of acute thyroiditis are frequently made in cases of simple hyperemia or hyperplasia of the thyroid.

CLINICAL TYPES

Hyperthyroidism and hypothyroidism in anything approaching advanced stages are unmistakable and the signs and symptoms have been described under these headings. The laboratory and other measures helpful in the diagnosis of atypical and borderline cases have also been described. As an aid for the general recognition clinically of these types, the following in tabular form is given:

HYPERTHYROIDISM	HYPOTHYROIDISM
Increased basal metabolism,	Reduced basal metabolism,
Increased nitrogen metabolism,	Increased carbohydrate tolerance,
Increased carbohydrate metabolism,	Lowered temperature,
Diminished carbohydrate tolerance (see text),	Shortened stature,
Delicate, soft, moist skin,	Irregular development of epiphyses of long bones,
Tendency to sweating,	Short, stubby fingers,
Fine lustrous hair,	Slow heart and pulse,
Rapid heart and pulse,	Thickened, infiltrated, dry, rough skin,
Palpitation,	Loss of hair or scanty, brittle, dry hair,
Tremor,	Mental dullness,
Emotional instability and mental alertness,	Slow movements,
Tendency to asthenia and fatigue,	Thinning of outer 1/3 of eyebrow.
Lymphocytosis (see also special eye signs),	Thickened mucous membrane of mouth and thick, enlarged tongue,
Long, slender bones,	Teeth irregular, poor quality, delayed dentition.
Long, slender fingers,	
Teeth white, pearly and well formed.	

PREPARATIONS, DOSAGE AND ADMINISTRATION

Desiccated thyroid, Thyroideum siccum U. S. P., is the only preparation in general use in medicine. It is also the only preparation in the U. S. P. It is an entirely satisfactory preparation with a long history of successful use. The dose is from 1/10 to 2 gr. t. i. d., depending upon the case requirement and the purpose of therapy. (See page 48.) For general "tonic" effects the dose should be from ¼ to 1 grain daily. For infants, 1/20 t. i. d., and for children, 1 grain. In cretinism the dose may be larger.

Other preparations sometimes used in medicine are: Iodo thyro globulin, described on page 49; the dried serum of thyroidectomized animals,—5 gr. capsules; the dried milk of thyroidectomized goats and 50% added lactose,—60 gr. to 1 oz. daily; Thyroxin,—one milligram; Thyroid nucleo protein, 1%, 5% and 10%,—1 to 2 tablets.

Oral administration is the only method in use. By it the thyroid effect is attained quantitatively, for the digestive action in the alimentary tract is without effect on ingested thyroid. Too high dosage is evidenced by the symptoms of hyperthyroidism (*q. v.*), and at the first evidence of such the dosage should be reduced or the administration temporarily discontinued. As is well stated by Williams,[a] gross symptoms of hyperthyroidism should not be permitted to develop in a carefully observed case. The early symptoms, such as a little looseness of the bowels, a little quickening of the pulse, a little increase in nervous excitability and the raising of the temperature to normal, should be signs for reduction of dose or discontinuance. As long as weight increases in long routine treatment the drug may be continued, and discontinued if the weight decreases. In obesity, of

course, a weight reduction may be expected. Williams lays stress upon the development of a coryza as a sign of overdose. Individual differences in behavior to thyroid substance are very common and may be marked. Thyroid should always be given first in low dosage and then increased.

THERAPEUTICS

From the nature of the physiological action of the thyroid and the effects of administered thyroid preparations discussed above, it is evident that it is a therapeutic agent with a wide field of application. It is, in fact, generally recognized as one of the most valuable substances used in modern medicine. Its action is constant and certain and the effects in some of its uses are the most definite, pronounced and satisfactory in all medicine. In proper dosage it stimulates metabolism and its effects are anabolistic—there is definite effect in tissue building. There is no known substance which will in like manner raise the basal metabolic rate and its action is, therefore, if used in proper dosage, truly tonic—the increased physiological oxidation aiding in the destruction of accumulated toxic waste and a low depressed physiological condition being changed to normal. Hoskins says:[108]

> "Another promising field for therapeutic investigation is the utility of thyroid as a non-specific drug. The thyroid hormone appears to be a general cell stimulant, and hence to be widely indicated in conditions in which depressed functional activity is a predominant feature."

The subjective feelings of the patient and the increased sense of well being are frequently very marked and accompany increased appetite and improved general nutrition. One great use of thyroid, therefore, is the treatment of such conditions as asthenia, general debility and low vitality, in which conditions, combined with other endocrine products, it has been found of definite and marked efficiency. (See page 233.) Sajous[44] outlines the general field of thyroid therapy as follows:

> "1. In diseases due to slowed destruction of toxic wastes, as shown by its action in tetany, epilepsy, eclampsia, disorders of menopause, asthma, chronic rheumatism, migraine, and also by those due to slow oxidation of fats, as in obesity.
>
> "2. In diseases due to lowered general nutrition of all tissues, including the bones, as shown by its action in hypothyroidea, cretinism, myxedema, and kindred disorders in which calcium metabolism obtains—osteomalacia, rickets, and osteomyelitis.
>
> "3. In disorders due to lowered nutrition of the muscular elements, including the skeletal and vascular muscles, as shown by its action in general adynamia, neurasthenia and myasthenia.
>
> "4. In all cases in which the processes of repair or absorption are deficient, as shown by its action in delayed union of fractures, certain benign and malignant neoplasms, and syphilitic tissue and bone necrosis.
>
> "5. In infectious diseases—owing to the increase of auto-antitoxin, thyroiodase (opsonin), and phagocytes—as shown by

its action in the early stages of tuberculosis, typhoid fever, infectious tonsillitis, and certain exanthemata."

Asthenia treatment, page 233.
Hypothyroidism treatment, page 233.
Myxedema treatment, page 72.
Cretinism treatment, page 227.
Goitre treatment, page 70.
Amenorrhea treatment, page 172.
Dysmenorrhea treatment, page 174.
Menorrhagia treatment, page 178.
Menopause treatment, page 182.
Senility treatment, page 238.
Delayed puberty—see amenorrhea, page 172.

Asthma Thyroid has been effective in some cases of asthma and has numerous mention in the literature. Osborne [65] states: "Not infrequently the asthma which occurs in old age is prevented by thyroid, perhaps because it aids in combating the irritation from malnitrogenous metabolism. At any rate, with high blood pressure associated with asthma, thyroid is of benefit." Halsey [66] says, "While to me at least it is very improbable that asthma is often of thyroid origin, there are certain reasons why it does not seem improbable that administration of thyroid may exert a favorable influence on it."

The increased oxidations and the destruction of toxic protein metabolites as a result of thyroid seem attractive in explaining its use.

Constipation Constipation has been shown to be a characteristic of hypothyroidism, and when this condition is present thyroid is of marked benefit. It is of doubtful value for constipation of other origin, but the prevalence of hypothyroidism in children makes it a very useful agent for this condition.

Enuresis The results of thyroid therapy in enuresis have been successful in the experience of a large number of observers.[67, 68, 69, 70, 71, 72, 73]

Enuresis may be a part of the general condition of hypothyroidism and due to a desquamation of epithelium around the neck of the bladder, as suggested by Hertoghe. However, no signs of generalized hypothyroidism may exist. Enuresis occurs frequently in children with adenoids, and these cases respond well to thyroid treatment. Dosage should be low ($\frac{1}{2}$ to $1\frac{1}{2}$ grs. daily).

Epilepsy There have been numerous reports of the value of thyroid in epilepsy. If the patient is hypothyroid, the chances of improvement are excellent. When hypothyroidism is not manifest, the chances are less. It is not to be expected that in a condition such as this, with its varied etiology, it will be effective in all cases. Osborne [74] says that many cases of epilepsy have their origin in the mouth and throat, and that after cleaning up these sources "The administration of thyroid extract and of calcium salts will always ameliorate and sometimes cure this type of epilepsy. Also, the epilepsies that are aggravated at the time of puberty, or are aggravated during pregnancy, should be managed on this same plan."

According to Sajous, the principle of treatment in epilepsy is "to activate the catabolism of spasmogenic wastes through the adrenal system." (Thyroid is a stimulator of adrenal activity.) * * * "Such remedies, (as stimulate the adrenal center) to keep the blood free of toxic wastes; dietetic measures, to reduce the quantity of such wastes formed; and finally, the free use of water, to insure the rapid elimination with the urine, sweat, etc., of all physiological wastes, constitute a therapeutic triad which soon causes the vasomotor center to lose its irritability, thus preventing the cortical hyperaemia to which the convulsions are due."

Growth In the lack of development and growth in children—mental and physical—thyroid is of general value. It is of particular value in those cases which show signs of hypothyroidism (see page 248), and in these the dosage may be raised; general defective development will usually respond better to pluriglandular therapy and a combination of Pineal, Thyroid, Anterior Pituitary, Suprarenal and Gonads (special formulæ 3 and 4) is advisable; this may be supplemented by additional thyroid if necessary.

Hemorrhage Some favorable reports have appeared of the use of thyroid in such conditions as hemophilia. In a case reported by Bottaro and Fournier,[75] thyroid was effective in controlling the hemorrhages in a girl, which were manifested as excessive menstruation, epistaxis, subconjunctival hemorrhage, hemoptysis, etc. If treatment was stopped, the hemorrhage returned. Réné Bernard[76] reports a case of hemophilia associated with myxedema, in which symptoms disappeared under thyroid treatment.

Infectious Diseases Thyroid administration is stated by some to definitely increase the immunizing power of the serum. Whether this is effected through the addition of antibodies to the serum or is a phase of metabolism is not definitely known, but that the removal of the thyroid lowers resistance to infection and that the administration of thyroid substance increases it is generally accepted. Sajous states that in surgical diseases, such as septicemia and erysipelas, and in suppurative processes, it is valuable in curtailing the disease. It has also been recommended in syphilis, particularly those cases (tertiary) which have resisted treatment. During the long continued administration of mercury and as a result of the syphilitic infection the thyroid function is frequently impaired, so that occasional courses of thyroid therapy would seem to be worth trial.

Obesity There are many causes of obesity, and they may be exogenous, endogenous, hereditary, endocrine, etc. There is a strong tendency in hypothyroidism to deposit fat, and in such cases thyroid therapy is of great value. Thyroid stimulates all metabolism and the oxidation of fat takes place as a part of this general effect; during its use for this purpose the protein content of the diet should be increased to compensate for the increased metabolism of proteins and to maintain balance. In obesity due to over-eating, the result will not be so good as in other types. In the obesity of the menopause it is of real value. In infantile obesity, which Osborne says is likely to be associated with pituitary deficiency, the thyroid may be combined with pituitary. "These

increasing the proteolytic activity of the blood, promotes destruction of the toxic wastes which underlie the disease." Leopold-Lévi and de Rothschild have found thyroid of the greatest value in treatment.[81] They state that arthritism is characterized essentially by a retarded metabolism, a chronic auto-intoxication, and that hypothyroidism and arthritism are manifested by the same symptoms. The infections also add their toxic products to the blood stream (Sajous), and it is well known that a history of an existing infection can be shown in the majority of cases of rheumatism. Thyroid administration, therefore, raises the metabolism, increases antitoxic and catabolistic functions of the body and removes the arthritic diathesis. Halsey[82] states, "I am convinced that I have greatly helped some of my patients with subacute or chronic arthritis, or with 'muscular rheumatism,' by giving them thyroid in doses of ½ to 1 or 2 grains daily."

Mutch[83] reported an analysis of 200 cases in which gout, venereal and tubercular disease of the joints, and all monarthrites, were excluded. Active sepsis was present in the nose and throat in 34% and around the teeth in 52%, while infective streptococci were found in the feces in 84%. Mutch lays stress upon infective organisms gaining ingress through the intestinal tract, and states that the condition of the alimentary tract dominates the outlook in rheumatoid- and osteo-arthritis. In treatment, after careful attention to accessible sites of infection and to the intestinal tract, autogenous vaccines and thyroid extract were used. Chronic infection damages the thyroid, and in Mutch's series minor forms of hypothyroidism were very common, while well defined myxedema or goitre was present in 14% of the cases. Thyroid extract was given in all such cases with great benefit to the joints. This series, which has been followed in some cases up to nine years, shows very great improvement or complete arrest in 89% of the cases. Couland[84] states that thyroid is of the greatest benefit in types of chronic rheumatism, and that treatment should be kept up for a long time.

Senility In the treatment of senility, thyroid is a mainstay. The discussion of this subject, (page 235,) shows the senile changes to be pluriglandular in character, with the thyroid as the central factor. Remarkable results are reported by Scott.[85]

Skin Disease In the treatment of the thickened, scaly, dry condition, characteristic of the hypothyroid state, thyroid therapy is very effective. Particularly in children are the results in this class of cases very good. In skin disease presumed to be due to deficient metabolism—dermatitis herpetiformis, prurigo, psoriasis and chronic eczema—thyroid is of value. The action in these cases is said to be as follows:[86]

> "1. Increased nutrition of the skin; hence its probable remedial action in ichthyotic conditions: an effect produced without any necessary abnormal perspiration.
>
> "2. Increased action of the cutaneous glands, accelerating excretion of waste-products, thus keeping the surface in a supple condition.
>
> "3. Regrowth of hair, as shown in myxedema and some cases of general alopecia.

"4. Increased activity of the epidermal layers, causing desquamation of unhealthy epidermis and reproduction of a new covering, as observed in ichthyosis, psoriasis, dry chronic eczema, and at times in myxedema and cretinism."

Thyroid is said to be useful in ichthyosis.[100] In urticaria it may prove of service. Fabini [87] reports a case of nine years' standing and resistant to all other treatment, which responded and was led to recovery under dietary restriction and thyroid therapy. This case showed other signs of hypothyroidism and the urticaria was interpreted as due to anaphylaxis, resulting from the liberation of toxic protein as a result of the faulty thyroid function.

The undoubted relation of hypothyroidism to cutaneous disturbances and the relation of the thyroid to the development of abnormalities of the skin appendages give a basis for a trial of thyroid in cases of skin disease which may be due to faulty thyroid function. Reports of essential changes in the skin and stimulation of the growth of hair during courses of thyroid therapy are not infrequent in the literature. In all of these uses, other than skin disease forming a part of demonstrable hypothyroidism, thyroid therapy is worthy of trial, although it is far from certain of success.

Toxemia

In toxemia resulting from absorption from a sluggish colon thyroid is of distinct value. Not only is the tone of the muscle of the bowel raised and the cause of the condition directly affected, but the action of the thyroid in disposing of and destroying the toxic absorbed products is brought into use. In toxemia, and particularly this type of toxemia, the thyroid is markedly affected and thyroid administration is definitely indicated. This is also true of the toxemias resulting from focal infection. In vomiting of pregnancy thyroid may be of value, and it has been found useful in eclampsia. "Puerperal eclampsia, in which the urine gives no evidence of insufficiency of the kidneys, has been attributed to thyroid disturbance, and certainly in these cases thyroid extract in very large doses has been successful in preventing and stopping convulsions." [88] The thyroid should, of course, be adjuvant to the general treatment of such a serious condition as eclampsia. Osborne states that the dose should be 10, 20 or even 30 grains in the first six hours.

Contraindications

Any symptoms of hyperthyroidism or thyrotoxicosis, mental excitement, too rapid metabolism or individual idiosyncrasy.

PART II

CHAPTER II

PARATHYROIDS

ANATOMY

The parathyroids were discovered in 1880 by Sandstroem, and are sometimes referred to as Sandstroem glands. This work was purely anatomical and the structures described were the external parathyroids, the internal not being discovered until a later date. Their function was first studied by Gley in 1891. In human anatomy the parathyroids are in close relation to the thyroid. The usual number is four, two of which, the superior parathyroids, lie on the posterior surface of the upper portion of the gland, one in each lateral lobe. This pair may be partially embedded in the substance of the thyroid, hence the name sometimes given—internal parathyroids. The inferior parathyroids lie on the posterior surface of the lower portion of the thyroid lobes and are termed the "external parathyroids." Additional parathyroids are not infrequently found. There is a great variation in this arrangement and number among different species and even in members of the same species, and frequently masses of parathyroid tissue are found embedded in thyroid tissue with no well-defined capsule or limiting connective tissue to distinguish them. The blood supply is from the inferior thyroid, which sends branches to the several glands. The venous return is by way of the thyroid veins. The nerve supply is not well known, but is apparently from the sympathetic.

The parathyroids are surrounded by a capsule, which holds together the masses of epithelial-like cells, divided roughly into lobules by a connective tissue network continuous with the capsule. The cells contain granules, some of which appear to be fatty. They are of two general types: one, the chief cells making up the main portion of the tissue, and the other, smaller and with a nucleus staining with hematoxylin, being perhaps a degenerative stage. In some instances colloid-like material is found between the cells, or where there is something approaching acinus formation, in the acini. The parathyroid apparently differs fundamentally from thyroid tissue in its inability to fix iodine. The method of entrance of the internal secretion to the system is unknown.

EMBRYOLOGY

The parathyroids arise as outgrowths from the entoderm of the third and fourth branchial clefts; the superior or internal arise from the fourth cleft and are sometimes called Parathyroidea IV; the inferior or external arise from the third and are the Parathyroidea III.

PHYSIOLOGY

The importance of the parathyroids in the animal organism is evident and beyond question. The precise function is still a matter of doubt. Two generally held theories are: (1) The regulation of the calcium metabolism of the body; and (2) The prevention of the accumulation of toxic products (Methyl-guanidin) by an influence on the metabolism of these substances which in increased concentration give irritative effects on the central nervous system and on the myoneural junction in the muscle substance.

Calcium Regulation Theory

The theory of calcium regulation was advanced by McCallum and Voegtlin,[89] and holds that the parathyroids in some manner control the metabolism of calcium and regulate its concentration in the body, and by this means influence the nervous system, the excitability of which varies with the calcium content—an excess depressing and a deficit increasing the excitability. Extirpation of the glands leads to a definite lowering of the calcium level, and administration of calcium salts relieves the chief symptoms of parathyroid extirpation—tetany. This theory, which has lost many supporters in favor of the guanidin detoxication theory, has recently received support from the experiments of Salvesen (see below).

Vines[320] has shown that calcium exists in the blood in an ionized and in a combined state, the combined calcium being concerned in coagulation, after which process the calcium of the serum is found to be in ionized form. In some disease processes he found some of the serum calcium to be the combined form after coagulation and a relative deficiency of ionic calcium. The administration of parathyroid substance restored the calcium of the serum to normal (see ulcers, page 88).

Detoxication Theory

While it seems established that the parathyroids are all important factors in calcium metabolism, certain facts point to an accumulation of toxic substances in the blood which give rise to the peculiar manifestations of tetania parathyreopriva; mere dilution of the blood by transfusion with physiological salt solution, or withdrawal of a quantity of blood by bleeding, is sufficient to control the symptoms, as well as the administration of other salts (strontium). The theory that the parathyroids are concerned in the metabolism of such substances is chiefly due to Koch and Paton and his associates.[90] Koch, Paton and his associates found a number of toxic substances, chiefly guanidin, methyl guanidin, cholin, trimethylamin, etc., in the blood and urine of parathyroidectomized animals, and Luckhardt and a group of workers[91] have found conclusive evidence that dogs in tetany are suffering from an intoxication, the toxic substances being water soluble. Massaglia[92] believes that the parathyroids have the power of neutralizing or breaking down into simple compounds the complex substances of catabolic activity, or those toxic substances accumulating in the blood in the toxemias of pregnancy, the puerperium, from the intestine and muscular fatigue. If parathyroid function fails, these substances accumulate and result in such conditions as eclampsia, uremia, etc. If this condition persists, the kidney and liver may suffer damage secondarily. Hammett[93] has contributed some experimental data showing a possible relation between parathyroid function

and creatin-creatinin metabolism. Creatin is an amino acid, containing a guanidin group, and would be a possible source of the toxic substance in tetany. Hammett's experiments show that the addition of parathyroid tissue to extracts of muscle tissue retards the increase of creatinin formation, which usually takes place during incubation. This occurs in acid, neutral, or alkaline mixture. " Since the maximum retardation effect of the parathyroids occurs in solutions buffered to neutrality while the maximum creatinin formation takes place at the same reaction, the conclusion is justified that this parathyroid effect is an expression of a direct influence of the parathyroids on creatin metabolism." The detoxication theory is based upon the assumption that the parathyroids control the metabolism of certain toxic products, guanidin chiefly, and prevent its accumulation in the tissue. When present in appreciable concentration, guanidin and methyl guanidin irritate the central nervous system and the myoneural junction in the muscle substances, and give rise to the peculiar condition of tetany.

I. Greenwald (Jour. Biol. Chem., Mar., 1924) believes that the guanidin intoxication theory can not be accepted without further proof. His opinion is based upon criticism of the evidence of the presence of guanidin derivatives in the urine.

Berkeley and Beebe suggested that the parathyroids elaborate enzymes which are factors in the intermediary nitrogen metabolism. They suggest that tetany may be due to toxic substances of metabolism. The conclusions of Dragstedt and Peacock[*] also support the detoxication theories, *i. e.*, that the glands function by some method of detoxication. " Poisons in the blood stream are removed or destroyed by the parathyroid cell. It is, of course, possible if not probable that the glands may produce some hormone capable of neutralizing such toxic bodies, or of stimulating some distant organ to such function." Their conclusions are that:

> " 1. Parathyroid tetany or depression is due to an intoxication.
>
> " 2. The responsible toxic substances come chiefly from the gastrointestinal tract. They arise through the activity of the proteolytic group of intestinal bacteria, and are probably for the most part protein split products of the nature of amines.
>
> " 3. The function of the parathyroid glands is to prevent intoxication by these poisons."

A practical result of this work is the suggestion that tetany may be delayed or prevented by dietary measures, which prevent intestinal toxemia and the formation of these poisons.

Experimentally, a condition in all respects resembling true tetany may be produced by the injection of guanidin compounds, and the blood of parathyroidectomized animals and of cases of true tetany contains a greatly increased concentration of guanidin. The serum of animals in which the parathyroids have been removed gives effects on a frog muscle preparation similar to those of guanidin. The increase and character of the nitrogenous compounds of the urine are similar in animals whose parathyroids have been removed and in normal animals receiving injections of guanidin. That the calcium regulation theory and the guanidin theory may be part

of the same process is suggested by the fact that, after injection of methyl guanidin into the blood, the calcium concentration is decreased (Watanabe).

There is still current among a few investigators [96] the theory that the thyroids and parathyroids are antagonistic in function. The theory holds that the thyroids stimulate metabolism and that the parathyroids have an antitoxic function, so that, as has been found by some, removal of the thyroids should give more pronounced symptoms than removal of both thyroids and parathyroids—a view not generally held.

The strong experimental evidence and the findings of clinical pathology make it appear that both of the functions of the parathyroids have been established. Whether they are interrelated and dependent upon each other is unknown. It is possible that a secondary accumulation of guanidin compounds is brought about by a faulty metabolism induced by too low calcium concentration, or there may be the exactly opposite relation. Both conditions may be subordinate to some more fundamental cause. The relation of either to the genesis of tetany is unknown.

Extirpation Experiments

One substantial element in the confusion of results of the early experiments in thyroidectomy was the failure to consider the parathyroids. This error maintained even after their discovery. Sandstroem's work merely pointed out the parathyroids as separate structures, and Gley's early work on their function was apparently not well known. Experimental difficulties in various species in removing accessory glands and the embedded parathyroids also confused the findings. Among the first experiments in removing the parathyroids (complete removal of the four) without surgical complication, etc., were those of Vassale and Generali. They noted that practically all of the parathyroidectomized animals died within a few days, with symptoms strongly suggestive of some mechanism involving the nervous system—tremor, paralysis or tetanic contraction of muscles, rigidity of the hind legs, incoördination of movements, convulsions, asthenia, dyspnea, rapid breathing and death. There was also involvement of the gastrointestinal tract, vomiting and loss of appetite.

These results have been confirmed by a very large number of workers, and today it is generally held that the parathyroids are separate functional units, that their function is distinct from that of the thyroid, that the functions of one are not performed by the others, that the tissue of one is not an embryonic form of that of the other, and the parathyroids are essential to life, and death results on removal, if all the glands and accessory bodies are removed. The number who dissent from any of these conclusions is small.

Parathyroidectomy results in more acute symptoms, and more rapidly appearing, in young animals than in old, extreme age apparently almost preventing the usual symptoms. The diet is also a factor, large quantities of meat in the food intake precipitating the onset of symptoms, and rickets appearing to predispose to symptoms of greater severity. The character of the calcium metabolism in old age and in rickets, and of the intermediary metabolites of protein metabolism make the facts of interest

when considered in relation to the two theories of parathyroid function—calcium regulation and the guanidin metabolism.

After parathyroid extirpation the calcium content of the blood and tissues is very markedly reduced. This was shown by McCallum and Voegtlin, and later by others. Salvesen [96] finds that the drop in calcium level is the characteristic feature of parathyroid insufficiency and is responsible for the symptoms of tetania parathyreopriva. "The symptoms of parathyroid insufficiency are due to calcium deficiency. The parathyroids control the calcium level of the blood and by doing so they influence the function not only of the muscle and nerve tissues, but probably of all the organs." It has been shown by many workers that the symptoms of tetany can be controlled by the administration of calcium salts (oral or intravenous), but the calcium is not retained and the calcium must be repeatedly administered. Salvesen has shown that the loss of calcium is almost wholly through the intestinal tract. The symptoms only reappear after calcium injection, when the calcium of the blood has reached the same low level as before. Milk in the diet controls tetany and prevents its appearance even when meat is added. The milk in these experiments contained 1.2 gm. per liter, the equivalent of about 10 gm. of calcium lactate, and this is the explanation of the effect of milk in preventing the appearance of symptoms. Four dogs in the experiment could be kept alive indefinitely on a milk diet and appeared normal in every respect, but tetany could be brought on at will by simply changing the diet to meat. Although the dogs appeared to be normal, the calcium content was low—below the normal for the animal. This is suggestive and is regarded by Salvesen as characteristic of latent tetany, as distinguished from cured tetany. The effect of calcium in prevenous), but the calcium is not retained and the calcium must be repeatedly cortex, and in lowering the excitability of muscle itself (experimental muscle nerve preparation), is well known, as are the effects of calcium salts in preventing the symptoms of tetania parathyreopriva and idiopathic tetany. Taken in connection with the known lowering of calcium in the blood in these conditions, it is strong evidence of some function of the parathyroids in calcium control. The later work of McCallum and Voegtlin and various co-workers strongly supports this view and that the symptoms of tetany are due to the calcium deficiency.

The main facts supporting the intoxication theory, with guanidin as the exciting agent, have been referred to above. It appears to be the most generally accepted, but may be closely related to the calcium regulation theory.

Feeding Experiments

Most of the experiments in feeding parathyroid substance have had as their object the control of the symptoms of tetany. The effects on general physiology are, therefore, not well known. Some studies have shown an increase in nitrogen metabolism, but the results are not striking. Parathyroid feeding (white rats), even with heavy doses, does not produce any definite effects on the growth of animals.[97] The effects on controlling symptoms of tetany will be discussed under Therapy.

TETANY

Tetany is today held by practically all to be due to disturbed function of the parathyroid glands, although the recent investigations of the subject have brought out factors in the condition and features of origin which are difficult to relate to the parathyroids, and suggest that tetany may not have a single origin. It is defined by Falta as follows:

> "By tetany we mean an abnormally increased condition of excitement of the nervous system, that is demonstrable in a heightened excitability of the motor, sensible, sensory and vegetative nerves, and under certain circumstances, in paresthesias, and bilateral intermittent, for the most part painful, spasms, with intact consciousness, or becomes manifest through phenomena of irritation on the part of the vegetative nerves. To the picture of tetany belong also trophic and certain metabolic disturbances. The manifestations are the result of an insufficiency of the parathyroid glands."

Tetania parathyreopriva is the condition resulting from extirpation of the thyroids, and is generally believed to be a very similar if not identical condition to idiopathic tetany in man. Clinically, tetany may arise spontaneously (idiopathic tetany, occupation tetany). It may occur endemically or epidemically, and appears to be influenced by the seasons. The etiology is unknown. It has been ascribed to mild ergotism as a result of contaminated rye bread when largely used in the diet. It has also been held to be in some way associated with goitre. Males between the ages of 16 and 25 are predominantly affected. In a series of 576 cases observed by Frankl-Hochwart, 402 occurred in the months of January, February, March and April. Among the cases there were 223 cobblers and 117 tailors.

Tetany frequently occurs during and following various infections. It is generally believed that the infection is simply the exciting cause and must be preceded by the tendency to tetany—latent tetany—to be effective.

Associated with certain diseases of the gastrointestinal tract there is sometimes found a form of tetany. The most common are cicatricial ulcer of the pylorus or duodenum, stenosis, malignant disease and some cases of dilatation. These cases usually occur during the tetany months. Explanation for these cases is difficult. There has been suggested a condition of alkalosis arising as a result of the digestion defect. Falta suggests an intoxication mechanism:

> "It seems, therefore, that in a group of these cases there is present only a relative insufficiency of the function of the parathyroids with, however, markedly increased demands on them; we should consider further the possibility that in high-grade stagnation in the gastrointestinal tract substances are formed and absorbed that increase the excitability of the nervous system so markedly that under the circumstances the action of the parathyroids no longer suffices; we must also assume, however, a certain predisposition of the individuals affected, as conditions of stagnation in gastrointestinal conditions are rather frequent, while complication with tetany is very rare."

Tetany of maternity and menstruation is frequently described and may be explained on the basis of unusual demands on the parathyroids. These cases also are more frequent during the tetany months.

Tetany may occur in early infancy, from 3rd to 20th month, or from about the 3rd year and later. This latter form is essentially similar to tetany in the adult. Pathologic changes in the parathyroid have been reported in such cases. Absorption of toxin from the intestinal tract may be a factor, and unbalanced diet has been suggested.

The pathologic findings in tetany support the parathyroid theory of origin. There has been described a condition, increased protein metabolism with increased urinary nitrogen, in which the percentage of nitrogen of ammonia and the peptid nitrogen is increased. There has also been shown to be an accumulation of toxic products of protein metabolism, chiefly guanidin. Falta states that "disturbances in carbohydrate metabolism are almost constant in the tetanic dogs." With Rudinger and Eppinger he found the glucose assimilation limits depressed in dogs but not in man. A vast number of observations have been made as to the calcium content in the clinical varieties of tetany, and there has been some lack of agreement in the results; but it may be taken as sufficiently established and generally accepted that the calcium of the body, including the blood and nervous tissue as well as other tissues, is definitely reduced in amount. The influence of other metals is undoubtedly important. While calcium and magnesium act as depressants to nervous excitability, sodium and potassium apparently act as irritants. Thus the disturbed ratio between these substances in the blood, by creating a relative excess of sodium and potassium over calcium and magnesium, might create a condition of tetany. Nervous excitability appears to vary directly with the ratio $Ca+Mg:Na+K$. This theory follows the fundamental work of Sabbatini and Jacques Loeb and J. B. McCallum on the antagonistic action of these ions.

Tetany has been observed following administration of sodium bicarbonate, and in such a case it may be that the sodium ion is increased to a point at which it acts as a nervous irritant, even though the calcium remains normal. An interesting observation is that of Collip and Backus,[98] that tetany follows over-ventilation of the lung. This may be related to the theory of causation of tetany due to a disturbed acid-base equilibrium, producing either an acidosis or an alkalosis which has much experimental evidence to support it. This was first formulated by Wilson, Stearns and Thurlow.[99] These investigations and those of Grant and Goldman [100] show an alkalosis preceding tetany, which may be supported by later acidosis. The theories of pathogenesis of tetany, as above referred to, may be classified under three headings:

1. Disturbance in the equilibrium between the calcium and magnesium ions on the one side, and the potassium and sodium ions on the other.
2. Disturbed acid base equilibrium.
3. Intoxication from such products of metabolism as guanidin and methyl and dimethyl guanidin.

These theories may subsequently be shown to be related parts of a single process.

Symptoms

Most of the symptoms of tetany relate to the increased excitability of the nervous system. The condition may be latent and its diagnosis depends upon occasional attacks and a variety of diagnostic procedures devised to demonstrate the increased excitability. In well-marked tetany there is the characteristic "attack" of irregular tonic contraction of various muscle groups. These contractions are usually painful and contribute the chief element of terror to the picture of tetany. After the typical spasms, Falta regards the increase in electric excitability as the most important symptom of tetany (Erb's phenomenon). This is best shown by use of the galvanic current. There is increased excitability shown by both the motor and sensory nerves. Certain characteristics of attitude and posture may develop. Among the more important are the "obstetrical hand," described by Trousseau, a position in which four fingers are crowded together, cone shaped, with the thumb crowded into the center. The carpopedal spasm occurs chiefly in children, and the fingers are spread out instead of closed together, as in the "obstetrical hand." There is an associated contracture of the feet. In these tetanic contractures there may be involvement of the intercostal muscles and those of the trunk, abdomen and diaphragm, and the smooth, involuntary muscle fiber in various parts of the body may be affected, giving rise to such symptoms as spasm of the stomach, urinary bladder, bronchial constriction and spasms of the heart muscle. The spasms are usually bilateral, but one-sided contractions may appear. The legs and feet are more often involved in children, and the contractures of the toes and ankle may be characteristic. A rigidity of the muscles of the face has been described as the "tetany face." It is said to be an early symptom. The immediate stimulus to these various contractures and spasms varies—emotional, traumatic, temperature, etc. They may persist for from a momentary spasm to a contracture of several hours.

Special Diagnostic Signs

1. *Erb's phenomenon.* Increased reaction of the motor nerves to the galvanic current. Most constant and dependable of all.

2. *Hoffman's phenomenon.* Increased excitability of the sensory nerves on electrical stimulation. Ulnar nerve usually used.

3. *Trousseau's phenomenon.* Production of the contracture of the fingers (obstetrical hand) in latent tetany, by application of a ligature tightly around the upper arms. Of great diagnostic value.

4. *Chvostek's sign.* Three related groups of contractures, depending upon the degree of the tetany, are described:

Chvostek I. Light percussion in the region of the external auditory meatus (pes anserinus) causes contractions of the muscles of the whole side of the face, closing the eyelids, contracting the alæ of the nose and corner of the mouth. Even light stroking may produce it. Not common in this degree.

Chvostek II. Tapping under the zygoma produces contractions of the alæ of the nose and muscles of the corner of the mouth. Common.

Chvostek III. Percussion in this case causes only slight twitching of the angle of the mouth.

5. *Leg phenomenon* (*Schlesinger*). Painful spasms in the leg, induced by flexing the hip joint with the leg extended at the knee. Arises in from a few seconds to several minutes. Regarded as of the utmost value and reliability.

6. *Arm phenomenon* (*Pool*). A similar phenomenon to the above. Contracture of the muscles of arm after forcible abduction.

General weakness usually follows the spasms. The prognosis is grave, death or permanence of the condition occurring in a large number of cases. In tetany in children this is particularly true. In tetany of adults, seasonal tetany, etc., true idiopathic tetany, chances of recovery are better, but these cases probably always remain latent.

Treatment

> "A rational therapy must strive to do away with the chronic disorder that underlies the outbreaks of tetany. This pathological disturbance consists, as we have seen, in a vice of metabolism, due in many cases at least to an insufficiency of function of the parathyroid glands. A rational therapy will, then, attempt either to restore the function of the parathyroid glands, or, if this be impractical, to resort to a substitution therapy. The route to follow in the parathyrogenous cases is obviously that of organotherapy * * *." (Barker.)

Transplantation of the parathyroid gland has given successful results. This is not available as a procedure in general practice, but the oral administration or injection has proved very successful in relieving the condition of tetany (Moussu, Vassale, McCallum, Clark, Hertz, Berkeley, von Eiselsberg). Berkeley and Beebe[101] showed that the active constituent of the parathyroids is contained in the nucleo protein portion, and this is sometimes used in medicine.

Parathyroid substance may be given alone or in combination with calcium salts. Calcium, either as chloride or lactate, may be given. In grave cases as much as 90 grains of the chloride may be given in a day. Several days may elapse in such cases before the calcium of the blood is brought to normal. For routine treatment, Parathyroid Compound No. 7 is the most useful; it contains 1/20 gr. of parathyroid, as well as 2 gr. of calcium lactate. For the immediate control of the spasms, morphine up to ¼ gr. and chloral hydrate up to 20 grs. may be given. Chloroform inhalation may be necessary. Hot baths are useful. The diet should be low protein and made up of cereals and fresh vegetables when possible. In children, cow's milk should be excluded from the diet. Good hygiene is essential.

CLINICAL TYPES

These are not striking unless the parathyroid disturbance has progressed to the development of well-marked signs, such as tetany face, spasmodic attacks, parathyroid attitudes, etc.

HYPERPARATHYROIDISM	HYPOPARATHYROIDISM
Chiefly evidence of disturbed calcium metabolism.	Varying degrees of symptoms of tetany—"obstetrical" hand, carpopedal spasms, convulsive seizures, excessive excitability of the nerves, laryngospasm, spasm of stomach, etc.

PREPARATIONS, DOSAGE AND ADMINISTRATION

Parathyroid is used in medicine as the desiccated substance. The dose is 1/20 to 1/10 gr. three times daily. In children the dosage should not exceed 1/20 gr. t. i. d. The nucleo protein is also used, in 5% tablets in the same dosage.

Oral administration is generally used. Solutions of the nucleo protein may be prepared for hypodermatic use.

THERAPEUTICS

Osborne says:[102]

> "We may sum up the uses of parathyroid extracts by stating that small doses of parathyroid may be of benefit in all cases of muscle irritability. The dose should be very small, and the frequency of its repetition or the length of time it should be given depends upon the condition for which it is used."

Chorea Reports of the successful use of parathyroid in chorea have appeared, and it may have some effect in controlling the symptoms. In cases of latent or mild tetany, mistaken for chorea, it should prove valuable. The same may be said for epilepsy, in which the reports of its use are encouraging.

Eclampsia and Uremia The use of parathyroid has been successful in the hands of some [113, 114] who have reported the results of its use. In view of the probable action of the parathyroids in neutralizing the toxic products of metabolism, it would appear worthy of trial. Remond and Menvielle [104] report its success in the treatment of uremic intoxication. "Parathyroid treatment is successful in overcoming the intoxication of uremia; its effects proceed from a favorable modification of the coefficient of Ambard: it acts principally on the group of non-urinary azotized products found in the blood. It exercises no toxic action."

Epilepsy The etiology and pathogenesis of true idiopathic epilepsy is still a matter for research and study. It is generally believed to be in part at least a condition having for its basis an inherent, degenerative, excessive irritability of the cerebral cortex; a constitutional lowered threshold for stimuli, resulting in explosion of motor impulse to slight stimuli. Many theories as to the cause of the exciting stimuli have been proposed: psychic, intestinal toxins, etc. An endocrine involvement of the ovary, pituitary and some other glands has been described, and there are undoubted cases of epilepsy with a direct relationship to such tissues. However, as a mechanism in the production of idiopathic

epilepsy, the parathyroids may be the endocrine glands responsible. The similarity to tetany and the possibility of a relationship has been suggested, and that both may be due to faulty function of the parathyroids.[106, 107] Other authors differentiate between the conditions, and the relation between tetany and epilepsy is still not clear.

Paralysis Agitans Numerous favorable reports of the use of parathyroid therapy have appeared. Berkeley in numerous publications has noted the favorable effects of parathyroid in this condition. In the New York Medical Journal (1916) he reports 60% to 70% of cases as greatly benefited.

Spasmophilia G. H. Clark[106] reports several cases of spasmophilia, in which the spasm and convulsive symptoms were very marked; 1/10 gr. of parathyroid t. i. d. gave progressive improvement, and its discontinuance after ten days was followed by an immediate return of the convulsions in violent form. Renewed administration of the parathyroid again controlled the symptoms.

Tetany Parathyroid is in general use in the treatment of this condition (see above). It is probably of much greater occurrence than is generally recognized, particularly in children. The following are quoted from the symposium on tetany—Meeting of the Southern Medical Association, November 13–16, 1922:[102]

> "I believe, if we were better informed on the interpretation of the aberrant form of tetany, we would find that it is rather common occurrence." (Engelbach.)
>
> "Fully 90% of all general convulsions occurring under two years of age are due to tetany." (Mulherin.)
>
> "It is common enough in infants, and latent tetany is more frequent than is generally believed. If tests for latent tetany are made, signs of it will frequently be found where they were not expected." (Barker.)

The administration of parathyroid substance in cases of these spasmophilic conditions in children, tetany, epilepsy, etc., is good practice. Many cases respond most favorably and the concurrent administration of Calcium Lactate is advisable. (See No. 7 Parathyroid Compound.)

Ulcers—Varicose and Gastric Grove and Vines[111] have found parathyroid of value in the treatment of chronic ulcers, varicose and gastric. In 100 cases they found a deficiency in ionic calcium of the blood, which was restored to normal by parathyroid administration and was also accompanied by healing of the local lesion, improvement of general health and increase in weight. As to the cause of these conditions and the effect of parathyroid therapy, Vines says:[112]

> "The common factors in both the conditions mentioned are a deficiency of ionic calcium, and presumably a chronic toxic state. In varicose ulceration one may suppose that the latter arises from a continued, though partial, failure of the circulation in the varicose areas, which causes an overloading of the blood with products of catabolism. In gastric ulcer, various chronic

toxic states have been assigned as the causative factor, either locally in the gastric mucous membrane or at a distance. But the beneficial effect of parathyroid therapy on these two factors, toxemia and calcium deficiency, and on the ulcerative condition which is symptomatic of them, would lead one to suppose that in these cases the parathyroid glands are at least partially deficient in function."

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PART II

CHAPTER III

ADRENAL GLANDS

(SUPRARENAL CAPSULES)

ANATOMY

These bodies, situated above the kidneys, are usually two in number, although accessory adrenals are not uncommon. They are of a yellowish color. The right is triangular, the left almond-shaped and usually the larger. They are about 1½ inches in length, ¾ of an inch in breadth and ⅛ to ¼ of an inch in width, and together weigh from 4 to 8 grams. They rest on their posterior surface on the diaphragm, and laterally on the kidney. The adrenals are found in most vertebrates. They are not found in some fishes (dipnoi) and seem to increase in importance as we ascend the animal scale. In higher vertebrates, the adrenals show a distinct division into two parts, the cortex and medulla, which are combined as an anatomical unit. These parts are, however, of different embryologic origin as the cortex is developed from the mesoderm of the genital ridges, while the medulla develops from neuroblast masses, which give rise to the nerve cells and the sympathetic ganglia. In elasmobranch fishes, the cortical portions are anatomically separate bodies, the interrenal bodies. On treatment with chromates, the cells of the medulla give a characteristic yellow-brown color called the chromaffin reaction. By means of this, masses of cells similar to those of the medulla have been located in other parts of the body. These cells have been found with much constancy in the sympathetic ganglia and along the abdominal aorta, and it is now common to describe all such cells as the "chromaffin system." The carotid bodies lie in the region of the bifurcation of the common carotids, between the internal and external carotids. They give the chromaffin reaction and arise embryologically from the same germinal cells as chromaffin tissue in general. They are small, but a few millimeters in length and breadth, and are surrounded by a capsule attached to the artery wall.

The coccygeal body, frequently classified as an endocrine tissue, does not appear to be either an epithelial or internal secretion structure.

In higher forms large masses of adrenal tissue (chromaffin) are found distributed elsewhere than in the suprarenal medulla. Accessory bodies of cortical structure are also found (interrenal bodies), and bodies composed of both cortical and adrenal substance are not infrequent. In man the suprarenal body is divided sharply into the cortex, composed of interrenal tissue, and the medulla, of adrenal or chromaffin tissue. Occupying an intermediate position between this and the lower forms, in which

these tissues exist as separately located bodies, is a class of animals (some fish, reptiles, birds) in which there is a conglomeration of the two, but not in definite layers.

Blood Supply

The arteries to the suprarenals are derived from the abdominal aorta and the phrenic and renal arteries. These branches anastomose and there is a very extensive capillary system. The suprarenals are among the most vascular organs in the body, and the blood flow to the suprarenals is only second to that of the thyroid. Burton-Opitz and Edwards[1] found an average flow of blood through the adrenals of dogs of 4.9 c. c. per minute per gram of gland. The veins unite in each suprarenal to form a central vein, and a connecting network of small veins connects the venous system of the suprarenal with that of the kidney. The veins on the right side join the inferior vena cava, and on the left side the left renal vein.

Nerve Supply

The nerve supply is from the sympathetic system through the splanchnics and also from fibers of the suprarenal plexus. The nerve endings probably directly stimulate cell activity. The splanchnic nerves, however, probably do not convey vasomotor fibers. This has been demonstrated by Gunning,[2] and is indicated by the work of Burton-Opitz and Edwards,[3] who measured the blood flow through the adrenals and found no change following splanchnic stimulation, if the general arterial pressure is maintained at constant level.

The center in the brain for adrenal action is believed to be in the floor of the fourth ventricle:[4]

> "We conclude that the reflex center for adrenal secretion is located near the upper or front edge of the floor of the fourth ventricle, and that it is subject to both excitatory and inhibitory nervous influences."

Stewart and Rogoff[5] find that after transection of the cord at various levels the epinephrin output may be unaltered or diminished. When diminished it may be due to spinal shock of the mechanism in the thoracic cord regulating the liberation of epinephrin. Stimulation of large sensory nerve trunks and strong psychic (emotional) states cause an increase in the liberation of epinephrin.

Embryology

The cortex and medulla arise from different embryologic layers and in both embryologic origin and the developed tissue appear to be physiological entities. The cortex develops from the mesoderm of the genital ridge and appears first at about the fourth week of embryonic development as a series of buds or projections of the cœlomic epithelium in the "adrenal zone," which later unite and form the adrenal body.

The medulla has its origin in the neural ectoderm, from which also arise the sympathetic nervous ganglia, and the two types of cell may be

distinguished early in development. Later the chromaphil cells penetrate the mass of cortical cells and eventually form the suprarenal medulla. Other masses of chromaphil tissue form the paraganglia—accumulations in the region of the sympathetic ganglia which are developed at about the same time from the remaining cells of this primitive sympathetic-chromaffin tissue. The chromaphil staining reaction is not evident in these cells in earlier stages, and in man is said not to be present until after birth.

PHYSIOLOGY

Extirpation Experiments

The study of the function of the suprarenals by destruction by specific cytotoxins, mutilation and excision has been undertaken. Death following ablation in the earlier experiments was probably due to shock, infection, injury of nervous structures, etc. With improved technique it was shown that an animal might survive extirpation of one suprarenal and that this was accompanied by compensatory hypertrophy of the one remaining. When both capsules are removed, the experimental animal usually dies within a few days at most.

In those cases in which life is prolonged beyond that time, it may usually be accounted for on the theory of the hypertrophy of the accessory bodies. In partial removal of suprarenal tissue, various results are noted and depend upon the total amount of the tissue removed and upon whether cortical or medullary tissue remains. Biedl found that if one-eighth of the total suprarenal tissue is allowed to remain the animal will live, if the part left were the cortex. He believes that there is sufficient evidence to conclude that extirpation experiments demonstrate that it is the cortical tissue which is essential to life. This is generally believed today and is expressed by Marine and Baumann[6] as follows: "All the evidence at present available indicates that the cortex is the important and the medulla the unimportant tissue as regards maintenance of life." There is evidence, however, that the secretion of the chromaffin tissue also serves valuable functions, although G. N. Stewart and J. M. Rogoff have shown that in cats[7] and dogs and monkeys[8] liberation of epinephrin from the adrenals is not indispensable to life and health. There is usually sufficient chromaffin tissue in the paraganglia and elsewhere to function in place of that removed by total extirpation of both suprarenals. The results of extirpation experiments lead to the generally held conclusion that the cortex is indispensable to life and that the medulla, while exercising some highly important function, may not be necessary for life.

The animals die as a result of extirpation with characteristic symptoms. There is general muscular weakness, loss of interest in surroundings, loss of appetite, lowered temperature and blood pressure. Paralysis or great weakness of the legs may occur, respiration becomes difficult and convulsions are frequent. It may be noted that extirpation experiments have not succeeded in producing the clinical picture of Addison's disease. Death may result in the experimental animal before some of the characteristic symptoms have developed. Those which may follow extirpation, however, are:

1. *Lowered metabolism.* This is usually marked in degree. The body temperature falls and is maintained by external heat with difficulty. C. Aub, J. Forman and E. M. Bright [9] found that adrenalectomy in the cat causes a reduction of 25% in basal metabolism a few hours after operation.

2. *Lowered blood sugar.* This is well marked, and injections of epinephrin fail to give the normal response of increased blood sugar (at least in normal degree).

3. *Gastrointestinal symptoms.* Gastrointestinal ulcers, diarrhea, constipation are common.

4. *Dyspnoea.* Respiratory failure and great increase in the number of respirations per minute usually develop some time before the death of the animal.

5. *Blood.* The composition of the blood is altered and an accumulation of toxins usually takes place.

6. *Muscular fatigue.* This is the most conspicuous symptom of adrenal insufficiency, and invariably develops. (See page 218.)

7. Symptoms referable to disturbance of function of the sympathetic nervous system are noted.

Feeding Experiments

The experiments of R. G. and A. D. Hoskins [10] showed that the feeding of suprarenal substance in young animals stimulates the growth of the testes.

Functions of the Suprarenal Body

It is not possible at the present time to formulate a theory of the function of the adrenal bodies as single organs. Their separate embryologic origin and the clinical and experimental investigations indicate that they are separate systems, although in man they are linked together anatomically. Theories have been advanced of the antitoxic or neutralizing function of the adrenals with respect to the products of metabolism (Abelous and Langlois), and other investigators have extended and elaborated on this, but, at the present time, such theories find little support. Abelous and Langlois found that the injection of blood from animals whose adrenals had been removed caused marked symptoms in normal animals (paralysis, asthenia, respiratory distress). Muscle extracts of adrenalectomized animals have been shown to cause symptoms of suprarenal insufficiency. W. J. M. Scott [11] found the resistance to morphine greatly diminished in adrenalectomized rats before hypertrophy of the accessory tissue took place. Others have shown lessened resistance to injected toxic substances, and the reaction of the adrenals to infection and toxin, attended by structural changes, is well known.

Function of the Cortex

There is little definite knowledge of the precise functions of the cortex. Aside from the extirpation experiments, which indicate that it is essential

to life, experimental methods have contributed little to our understanding of the subject. There is much evidence, however, that the cortex plays some important part in the growth of the body and the development of the sexual organs. The suprarenal cortex, hypophysis, gonads and thyroid are apparently closely interrelated in the growth processes of the body and in the psychic development. Clinical pathology has been the chief method of investigation of such facts. Apart from the earlier theories of the detoxicating function of the entire adrenal bodies, there is some evidence that the cortex does exercise such a function. Myers [13] found that the venom of the cobra is neutralized or has its toxicity destroyed on mixture with an emulsion of the suprarenal cortex, but not with one of the medulla. Lewis found that white rats deprived of all suprarenal tissue died from a dose of cobra venom 5 to 10 times smaller than their controls; of curare of a dose ½ as large as the controls; of veratrine 7 to 10 times smaller than the controls, and of morphine 400 to 500 times smaller than the controls.[13] Moreover, marked structural changes of the cortex are noted in metal poisoning and in infective toxemias. The richness of the lipoid content of the cortex has given rise to another theory of its function, that of formation of the body lipoids. In the cortex are found lipoid substances of various kinds and a doubly refracting substance (lipoid) apparently mainly lecithin and cholesterol esters. The possibility of a lipoid formed in the cortex being used in the development of the myelin of medullated nerve fibers has been suggested by Schäfer, and it is one important theory that the adrenal cortex is a factor in the development of the highly organized nervous system of man, particularly the brain. In the normal embryo the cortex is greatly enlarged, but in anencephalous monsters the cortex or the characteristic boundary zone is absent. Evidence of a relationship between the sex glands and the cortex is shown by the enlargement of the cortex during pregnancy; by the small cortex in deficient sex development; by its hypertrophy in sexual precocity; by its hypertrophy after castration and by the changes in the cortex during œstrus in animals. Suprarenal feeding accelerates the growth of the testes (R. G. and A. D. Hoskins). Neoplastic growths (particularly hypernephromata) of the cortex are usually associated with sex abnormalities. There is also a theory that the preliminary stages in the synthesis of epinephrin take place in the medulla, but there is almost no experimental work to support it.

In addition to the effects of epinephrin in muscle metabolism and efficiency, the cortex also appears to exert some function in maintaining a normal physiological activity. Vacuole formation takes place in the cortex after prolonged muscular effort and may be due to excessive functional effort in producing some substance directly concerned in muscle metabolism (or in producing epinephrin).

The adrenals also play some important part in general metabolism. Destruction by freezing or ligation results in a disturbed metabolism and a marked increase in heat production.[14, 15] The evidence available points to the cortex as the portion most concerned in this increased heat production, but a function of the medulla in this phenomenon can not be wholly excluded.

Function of the Medulla

The constant presence of an active substance of definite chemical composition in the adrenal medulla, giving constant and characteristic effects on blood pressure after injection, has given rise to two general conceptions of its function: the "tonus" theory and the "emergency" theory. A respiratory function is also possible and has some strong evidence in its support. (See Blood and Respiration, page 104.) The "tonus" theory assumes that there is a steady and constant liberation of epinephrin in small amounts, at all times and in all physiologic states and that the quantity thus liberated is sufficient to maintain normal arterial tone by establishing a state of receptivity to stimulation by the sympathetic. It has been shown[18] that the rate at which epinephrin is liberated remains practically constant, although the rate of flow of blood through the adrenals may vary greatly, the concentration of epinephrin in the blood leaving the adrenal vein varying inversely as the flow. The tonus theory is not generally held now. In the minute quantities in which epinephrin could be present, the evidence is clear that the action would be of dilatation and not of contraction. Such a hypotensive action has been thoroughly demonstrated.[21] Furthermore, it is doubted by many that, under normal conditions, there is a constant liberation of epinephrin into the blood or that normal tone of the arterial system is dependent upon such epinephrin.

Respiratory and Tonus Theories

Emergency Theory

It has been shown by various experiments that an outpouring of epinephrin is effected by stimulation of the splanchnics,[18] and Cannon has formulated the so-called "emergency" theory of adrenal function. As is stated by Vincent,[19] it seems impossible to avoid the conclusion that when powerful impulses are transmitted along certain afferent nerve paths the adrenal medulla responds by epinephrin production, which plays a part in the blood pressure effects. It is not accepted without question, however, that in normal physiology the natural nerve impulses are sufficient to produce such effects. In publications in 1911[20, 21] it was demonstrated by Cannon that epinephrin was secreted during periods of emotional excitement, pain and asphyxia. Subsequently, the action of epinephrin in diminishing muscular fatigue and lessening the coagulation period of the blood was shown. It was conceived that such emotional disturbances as excitement, pain and asphyxia occur as an accompaniment of struggle, and that the outpouring of epinephrin would serve a valuable function in enhancing great muscular effort. The experiments referred to were made by withdrawing blood with a catheter pushed through a nick in the femoral vein and thence up through the vena cava to the entrance of the lumbo-adrenal veins. The epinephrin content was assayed by observing the effect of a preparation on rhythmically contracting segments of rabbit's intestine. Blood removed before stimulation of the central and of the sciatic nerve caused no inhibition of the segment of intestine, but that removed afterward caused relaxation. This seemed to prove that an outpouring of epinephrin is caused by stimulation of the adrenals through nervous pathways. Blood drawn in the same way, before great emotional excitement was caused in the animal, gave no

effects on the strip of intestine, while that removed after such excitement was produced caused inhibition of the rhythmically contracting strip. It had also been shown [22] that in a certain species of toad the melanophores of an area of denervated skin showed contraction following states of excitement, but, if the adrenals were previously removed, this did not take place. Some criticism of the method used by Cannon and his co-workers has been advanced (Stewart and Rogoff). These have been answered in detail by Cannon [23] and new evidence, using an entirely different experimental method, was presented, which appears to confirm his previous statements. These later experiments were made using the denervated heart as an indicator to show an increase of epinephrin in the blood. By this method, with the vagi cut and stellate ganglia excised, stimulation of the central and of the cut sciatic causes an increase of as much as 50 beats per minute. Such results, compared with those obtained by injections of epinephrin, give an estimate of the amount of epinephrin liberated per minute—an amount calculated at from 5 to 25 times the amount estimated as the normal outpouring. This increase of heart action does not occur if the adrenals are removed. Marked increase in the heart rate was also shown during asphyxia and excitement. Cannon sums up the "emergency" theory briefly as follows: "Excitement, pain and asphyxia are, in natural existence, commonly associated with violent struggle for self-preservation. Under such circumstances, as have been emphasized in the presentation of the 'emergency' theory, the operation of the sympathetic division of the autonomic system together with the aid which adrenin affords will muster the resources of the organism in such a way as to be of greatest service to such organs as are absolutely essential for combat, flight or pursuit." The primary nervous stimulus causing the physiological changes necessary for assembling the animal's resources are furthered and continued by the secondary liberation of epinephrin, which accentuates the action of the vegetative nervous system in putting the organism in a condition of quick reactivity and makes possible a quick expenditure of energy to meet the needs of the environment. Vincent,[24] in a study of the epinephrin effects on blood pressure, gives support to this theory. His results give evidence that the general effect of the liberation of epinephrin into the circulation in amounts in excess of that normally taking place would be to cause vasoconstriction in the skin area and vasodilatation in the skeletal and cardiac muscles. He says: "It is obvious that this might be of advantage in certain physiological emergencies. It seems probable that the chromaphil tissue, especially perhaps the so-called 'medulla of the adrenal,' may have important functions connected with the distribution of blood in the body, if not under normal conditions, at any rate in times of nervous and muscular strains." The evidence presented by Cannon seems to prove his theory, although at the present time it can hardly be held to be finally established. Stewart and Rogoff [25] hold that the denervated heart can not be regarded as an indicator of epinephrin liberation, as they state that a positive reaction (acceleration of heart) may be obtained when the epinephrin output from the adrenals is abolished by removal of both adrenals (in cats). They make no attempt to explain the acceleration of the denervated heart by sciatic stimulation. Cannon [26] recognizes that

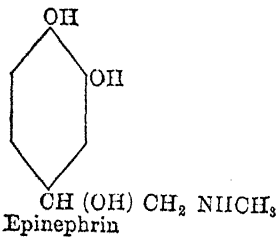
acceleration of the heart may be effected by splanchnic stimulation after adrenalectomy, and explains it as due to some agent arising in the liver. He has shown that the effect is slight in the fasting animal and much greater if the animal is digesting meat. He holds that this will account for the very slight effects on the denervated heart after adrenalectomy reported by him in 1919, as these animals were deprived of food for a day or so prior to the experiment.

The function of epinephrin in muscle metabolism and in maintaining muscle efficiency and relieving fatigue effects is described on page 218.

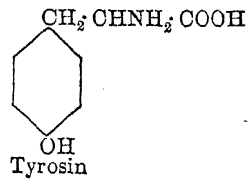
The opinion is held by some that epinephrin is not a hormone at all and that the adrenal medulla is not an organ of internal secretion, epinephrin being simply a waste product. Others believe that the medulla synthesizes epinephrin from intermediate waste products of metabolism, and through this agency regulates synthetic activity.

Epinephrin

Oliver and Schäfer in 1894[27] reported the effects of suprarenal extracts in raising blood pressure, results which almost immediately afterward were also reported by Szymonowicz and Cybulski, and the extraction of a pure chemical substance from the crude extracts at once became an interesting problem. In 1901 Takamine isolated in crystallin form the substance now generally known as epinephrin. It was also, about this time, isolated by Aldrich and later (1903) by Abel. Abel and von Furth had made many experiments before this and contributed valuable data bearing both on the nature of the product and methods of preparation. Some difference in the empirical formula was given for the product of the early workers in the field. The formula of Aldrich is now believed to be correct and the constitutional formula as determined by Jowett is generally accepted. This is dioxyphenylethanolmethylamine, resembling in structure tyrosin, from which it may be derived. The substance has been synthesized by Stolz, Dakin, Friedmann and Flächer.



Epinephrin



Tyrosin

Epinephrin is an optically active substance, that found in the body being lævorotatory. It has been prepared synthetically, the product resulting being a racemic compound which may be separated into a dextro- and a lævorotatory base by a reaction with tartaric acid and the preparation of the bitartrate. The racemic compound may also be separated by the action of Pencillium glaucum. The dextro-form is stated to possess but 1/12 the physiological activity of the natural form.

Epinephrin has a melting point of from 201 to 212 and melts with decomposition. It is but slightly soluble in cold water or alcohol, and is insoluble in ether. The salts of epinephrin, however, are readily soluble in water. The solutions are easily oxidized in the air and must be preserved in ampoules or tightly stoppered bottles. Some preservative is usually added.

Pharmacology of Epinephrin

Epinephrin exerts its characteristic effects through peripheral stimulation of the sympathetic nervous system. The effects are, therefore, manifest in all structures innervated by this system (except sweat glands) and are chiefly the result of stimulation of the nerve endings in the smooth, unstriped muscle. The work of Langley and of Elliott [28] has definitely established this general mechanism of epinephrin action and the effect of epinephrin stimulation of an organ or tissue is held to be the same effect exactly as that produced by stimulation of its sympathetic nerve supply. The locus of action is shown in the interesting experiment by Biedl on the heart of the chick embryo. Before the formation of the sympathetic elements in the embryo heart there was no response to epinephrin; after the development of these elements, however, epinephrin caused contraction and single arrhythmic beats. The effects of epinephrin may, therefore, be either of increasing or decreasing the activity of a tissue, depending upon its nerve supply (augmentory or inhibitory). This type of action through the sympathetic is called "sympathomimetic." As epinephrin is very readily and rapidly oxidized, even injections into the blood stream are of very fleeting effect. Administered orally, the larger part is probably at once destroyed, as the oxidation occurs in the intestine as well as in other tissues. The concentration of epinephrin in the blood in normal conditions is very small. The concentration in the arterial blood has been estimated at about 1 part in 1,000,000,000 (Trendelenburg). In the blood of the suprarenal vein there may be as much as 1 part in 1,000,000 to 1 part in 360,000. Epinephrin is contained very largely in the plasma. The average discharge of epinephrin (for cats) is calculated (Stewart) at 0.00025 mgm. per kilogram of body weight per minute.[29] Strychnine causes a marked increase in the liberation of epinephrin.[30] The very low concentration of epinephrin in the blood and the very minute quantities in which it is liberated have rendered its function in normal physiology difficult to determine. Its several pharmacological effects are as follows:

Circulation. Directly introduced into the veins, it causes prompt and marked rise of blood pressure which is of short duration. The chief factor in this rise is the remarkable vasoconstriction effect, and secondly the indirect stimulation of the vagus and the cardio-accelerator mechanism. Some few blood vessels (coronary, cerebral, pulmonary) respond normally by dilatation (which may be passive and secondary), and in very low concentration other vessels as well are dilated instead of constricted.[31] Cannon and Lyman [32] also showed that epinephrin might either raise or lower blood pressure, and that an amount of epinephrin which would lower the pressure in a normal animal would exert a pressor action in an animal with pre-existing lowered pressure. The depressor action has been attributed to

vasodilator nerve endings in the vessel wall,[33] and to a vasomotor center in the central nervous system.[34] J. B. Collip[35] has shown that the pressor and depressor action may be varied by varying the H+ion concentration. F. A. Hartman, L. G. Kilbour and L. Fraser[36] produced dilatation of vessels of the hind limb and of the intestine by the action of epinephrin on sympathetic ganglia and the superior mesenteric ganglion. They are led to believe from these observations that the sympathetic system contains vasodilator fibers to the intestine and to the hind limb. C. M. Gruber,[37] on the other hand, finds that small doses of epinephrin produce active vasodilatation in muscles in which the nerves are cut and allowed to degenerate from 2 to 10 days. He finds that "the vasodilatation in muscles caused by small amounts of adrenalin is dependent upon the tonicity of the vessel wall. Small doses of adrenalin (0.5 c. c. 1:100,000) bring about vasodilatation by their action on the peripheral vasodilator mechanism."

The characteristic constrictor effect (almost invariably following large doses) seems to be wholly dependent upon peripheral action, as it takes place after severance of all nerve pathways and strips of artery immersed in epinephrin solution show contraction. The pulmonary circulation is not greatly affected by epinephrin.

Heart. Epinephrin exerts a pronounced stimulatory effect on the heart, due to the action of the sympathetic nerve endings. Very frequently there is a slowing of the heart rate, due to vagus stimulation, although the heart force is strengthened. Usually in man, however, there is acceleration. Perfusion of the excised heart accelerates its action and causes increased amplitude of the beat.

The slowing of the heart which sometimes occurs, chiefly in animal experimentation, may be due to an effect on the cardioinhibitory (vagus) center, resulting from the increased blood pressure, although some experiments seem to show that this is not the only factor. The rise in pressure is much more marked if the inhibiting influence is removed by the administration of apocodein or by resection. When this is done, epinephrin causes increase in rate, as well as force of the heart action. So pronounced is the stimulatory effect on heart muscle, that excised heart muscle may be made to contract rhythmically hours after it has stopped beating. Clinically, the direct application to the infant heart has started the heart beating after failure of all other means.

Kidney. The vessels of the kidney show a tendency to constriction in a degree beyond the other blood vessels of the body. It has been demonstrated[38] that the subcutaneous injection of epinephrin in certain amounts (smaller or larger amounts fail to give the effect) increases the activity of the kidney, as shown by increased excretion of urea. This group of workers, after long and extensive research on urea excretion, have formulated the following hypothesis, based in part upon the fact as shown by them that epinephrin increases the urea excreting activity of the kidney and pituitary extract depresses it:

> "1. The subcutaneous injection of amounts of adrenalin which increase the urea excreting activity of the kidney, and of amounts of pituitrin which depress that activity, have no effect when they are injected together in a certain balanced proportion.

"2. All grades of stimulation or depression may be induced by the injection of mixtures of adrenalin and pituitrin in which this balance is deflected by a preponderance of one or the other.

"3. In the rabbit the removal of both suprarenal glands is followed by a depression of the urea excreting activity of the kidney, which is greater than that which follows similar operations in which the suprarenals are not removed.

"4. The facts in regard to urea excretion given in these and other papers are reviewed and from them the conclusion is reached that under physiological conditions the urea excreting activity of the kidney is determined by two main factors. There is a fixed and mechanical regulation through the urea concentration of the blood, but there is also another and overruling type of regulation which acts through the medium of the central nervous system.

"5. The mode of action of the regulation through the nervous system is discussed and it is suggested that variations in the balance between the rates of secretion of active principles from the suprarenal and pituitary glands may play a part in the mechanism through which it acts."[39]

Epinephrin may produce dilatation of the kidneys in some individuals, although this is usually preceded by brief constriction.[40]

A. N. Richards and O. H. Plant[41] find that epinephrin in very weak concentration decreases blood flow through the kidney, while the kidney volume and flow of urine are increased. They believe that this is evidence of a slight constriction of the efferent vessels, with consequent increase in glomerular pressure. This would indicate a mechanism for the regulation of urine excretion through the rise of pressure in the glomerular capillaries, as a regular constriction of the efferent vessels over the afferent vessels would raise glomerular pressure and permit of greater expression (or secretion) of urine if this is regarded as a filtration process. This view is advanced by the authors in a previous paper.[42]

Muscle. Epinephrin plays some essential part in voluntary muscle activity (see page 218), and seems specially concerned in the prevention of fatigue.

Smooth, unstriped muscle, innervated by the sympathetic, usually reacts to epinephrin. The muscles of the hairs, although smooth, unstriped and supplied by the sympathetic, usually fail to respond.

General Metabolism. The effect of epinephrin in the quantities in which it is used in pharmacological investigation is to definitely raise metabolic rate and body temperature. Boothby and Rountree[43] found that it regularly caused a definite (over 10%) elevation of the basal metabolic rate, and that it has a pronounced calorigenic action reaching a maximum within a few minutes. Tomkins, Sturgis and Wearn,[44] and Sandiford[45] have also demonstrated a constant rise in the metabolism, arising within a few minutes after injection of large doses of epinephrin, and Aub has reported[46] that removal of the adrenals in cats is followed by a rapid reduction of the metabolic rate. Boothby and Sandiford[47] also find subcutaneous injection of epinephrin attended by invariable increase in heat production, and usually by increase in the respiratory quotient. They believe there

is no relationship between the character of the reaction induced by epinephrin and the activity of the thyroid gland. They suggest as a cause an excess of carbohydrate metabolites or direct cellular stimulation of cellular combustion. The latter mechanism is also advanced by E. G. Martin and R. B. Armistead,[48] as a result of experiments on isolated muscle tissue. Marine and C. H. Lenhart[49] also find that epinephrin causes a rise in oxygen consumption in normal and thyroidectomized rabbits. They believe, however, that there is a lessened effect in thyroidectomized animals. Epinephrin has little effect on nitrogen elimination.

Sugar Metabolism. Large doses of epinephrin, injected into the circulation, produce hyperglycemia and glycosuria. Following such large doses glycogen disappears from both the muscles and the liver. Stimulation of the nerves to the liver causes a hyperglycemia, but if the suprarenals are removed no such effects are observed, and it has been held that stimulation of the splanchnic nerves and sugar puncture produce their effects through the stimulation of the adrenals, through the sympathetic system, and the consequent liberation of epinephrin. The action of epinephrin in these cases is assumed to be antagonistic to that of the pancreas, but the relationship between adrenals and pancreas in normal sugar metabolism is far from clear. Epinephrin (in large doses) either stimulates the production of sugar from glycogen or interferes with glycogen storage. It is probable that the glycosuria results from a sweeping out of the glycogen of the liver, primarily by its conversion into dextrose (glycogenolysis). When the liver has previously been exhausted of glycogen by phlorizin, or its functional activity prevented by phosphorus, epinephrin glycosuria does not occur, and in well fed animals with livers rich in glycogen both the hyperglycemia and glycosuria are increased. That epinephrin is the sole or even the principal agency in the normal physiological storage of glycogen and liberation of glucose is not believed. Stewart and Rogoff[50] experimentally prevented practically all epinephrin output and found no effect in the glycogen of the liver and that hyperglycemia following sugar puncture was not interfered with. They state that the hypothesis, that piqûre hyperglycemia is caused in the same way as the hyperglycemia caused by the injection of epinephrin, must be abandoned, as there is no real evidence that piqûre increases the rate of liberation of epinephrin from the adrenals.

Lungs. Epinephrin appears to bring about relaxation of the smaller bronchi, and thus relieves attacks of bronchial asthma.

Uterus. Large doses injected into the circulation cause strong uterine contractions. In pregnant cats contractions are produced and relaxation in the non-pregnant.[51] As has been suggested in the case of pituitary solution, epinephrin appears to sensitize the uterus to stimulation by other agents.

Pupil. In frogs, epinephrin has a definite mydriatic effect. In man, mydriasis is not readily produced except after excision of the superior cervical ganglion and degeneration of the sympathetic. This fact seems to prove a peripheral action. It may occur, however, after intravenous injection. Increase in the mydriatic reaction occurs in hyperglycemia.

Intestine. The typical epinephrin effect on the intestine is one of relaxation and peristalsis is usually inhibited. Hoskins,[52] however, has shown that small doses increase contraction and peristaltic movement.

Blood and Respiration. Epinephrin causes an increase in the consumption of oxygen in normal animals.[53] M. L. Menten has shown that the addition of epinephrin (base) to diluted human venous blood causes an increase in the intensity of the oxyhemoglobin absorption bands, and a similar result is obtained when adrenal vein blood is added.[54]

These and other observations tend to confirm the thesis advanced 20 years or more ago by Sajous, that the adrenals are directly concerned in respiration. Menten suggests that epinephrin can "act as a substance altering the property of hemoglobin so as to give it a greater attraction for oxygen as it passes through the lung." The observation of Cannon, that epinephrin is liberated in greater quantity in states of asphyxia and lack of oxygen, is also confirmatory. Professor Sajous early postulated such a function and the term "adrenooxidase" was introduced by him to describe this active substance.

HYPERADRENALISM

Hyperadrenia—Hyper-Suprarenalism

The physiological states accompanying rage, fear, asphyxia, etc., in which there is believed to be an excess of epinephrin over the normal liberated into the blood, have been referred to. These are temporary conditions. Lasting chronic conditions of this kind are not found in clinical medicine. The states resulting from tumor formation and growth resulting in increased function are rare. Atheroma, as is well known, may be produced by long continued injection of epinephrin. That epinephrin, in the amounts in which it is liberated in the blood even in the greatest concentration recorded experimentally, can have an effect in producing atheroma seems doubtful. In diabetes mellitus there is some increase in adrenal activity. "In many cases of diabetes mellitus, and especially in advanced cases, much speaks for the view that here also there is a slight overproduction of adrenalin."[55]

The relation of an assumed hyperfunction of the adrenals to interstitial nephritis and high blood pressure has not been satisfactorily demonstrated.

For all these states of hyperadrenalism pancreas therapy is indicated.

In general, high adrenal functional activity is associated with robust health, muscular efficiency, energy and somatic and psychic capacity. Pathologic hyperadrenia is not common.

Virilismus and Hirsutismus. Increased function of the suprarenal cortex in females, sometimes due to hypernephroma, gives rise to the condition of virilismus or hirsutismus. In this condition the male characteristics develop in the female, sometimes to a marked degree. If it develops before puberty, menstruation does not occur. It is characterized by obesity, sometimes by unusual strength, deep voice, rough and pigmented skin, excessive hair development. After puberty, in females who have been previously normal, there is cessation of menstruation, obesity, deepening of the voice, atrophy of the breast, development of the male figure contour, excessive development of hair over the body, with male type of distribution of pubic hair, and dry, wrinkled skin.

HYPOADRENALISM

HYPOADRENIA

(See page 220)

ADDISON'S DISEASE

The publication by Thomas Addison in 1855 of his investigations in the disease which now bears his name was important from the standpoint of endocrinology in general. The disease was well described by Addison, and the views held today are essentially the same as those of Addison, or those introduced shortly thereafter by his contemporaries.

SYMPTOMATOLOGY

It is a disease of middle age, arising usually in the third and fourth decades of life. Females seem to be more subject to it than males. It develops gradually, with general asthenia, lack of interest and malaise. The blood pressure is low and the temperature usually subnormal. The blood usually shows a lessened number of erythrocytes and lowered hemoglobin index, although these blood changes are regarded by some as inconstant. Addison himself first described the condition as "idiopathic anemia." Digestive disturbances are common with vomiting or diarrhea and constipation, which may be alternating in character. Nervous symptoms (twitchings, diminished knee jerk, etc., psychic and emotional abnormalities) frequently occur.

Asthenia Asthenia is the most characteristic of all symptoms of Addison's disease. It develops in most pronounced degree and the patient is always tired and unable and disinclined for any physical effort. This symptom has been attributed to deficiency of both the cortex and the medulla. The weight of evidence is in favor of deficiency of the medulla. Asthenia is the earliest symptom arising in Addison's disease, and should be carefully sought for. Sezary [56] emphasizes asthenia as the most reliable of all the symptoms of Addison's disease, most of which are not characteristic, and even when associated have no specific diagnostic value. Muscular fatigue is the most reliable of all. He lays stress on the importance of ascertaining whether the muscular fatigue has existed since the beginning of the disease.

Pigmentation Pigmentation is the symptom second only in importance to the asthenia. It usually occurs later, and is somewhat less constant (occurring, however, in about 75% of cases). It may appear in any site in the body and on both skin and mucous membranes, but is more common on face and neck, back of the hands, lips, anal folds, knuckles and surfaces which have suffered some irritation. The linea alba seems especially subject to pigmentation. The discoloration may begin as a general darkening of the complexion. The color is at first yellowish, later turning to various shades of brown and then bronze or very dark brown. The pigment is found in the rete Malpighii and is iron free. The cause of the pigmentation is not satisfactorily explained, although several theories have been advanced. One holds an excessive activity of the cells

of the Malpighian layer, resulting from excitation through nervous pathways. Another assumes that epinephrin is manufactured from tyrosin as a preliminary, intermediate product. When adrenal function fails, tyrosin is not converted but accumulates, and that which finds its way into the skin and is exposed to light and oxidation changes to a dark color. Melanin has been shown to be synthesized in this way (from tyrosin), and it is possible that the excess of tyrosin results in greater melanin production. It has also been suggested that melanin may be formed as a result of the action of oxidases (contained in the epinephrin) upon tyrosin and similar compounds.

Heudorfer[67] has suggested that the skin may be something more than a protective covering and may supply an internal secretion. According to this view, pigmentation in Addison's disease is due to compensatory activity of the cutaneous epithelium to replace the lack of secretion by the suprarenals. The isolated skin pigment has a vasoconstricting action and affects the sympathetic nerves in a like manner to epinephrin.

Etiology and Pathogenesis

Addison's disease is today regarded by most investigators as due to hypofunction of the adrenal glands, which may approach complete functional inactivity. It develops gradually and early diagnosis is usually not made. The condition, however, may be acute. The cause may be found in tuberculosis of the adrenals, which may be either primary or by extension from adjacent tissues. Hemorrhage into the gland may be the cause. Constitutionally defective adrenal apparatus has been assumed as a cause for the susceptibility to decreased function. The decreased function of the adrenals may act in producing Addison's disease through the failure to maintain the necessary concentration of internal secretions which is required in normal physiology. This may be the lack of production of epinephrin, which is shown on page 218 to be so essential to muscle efficiency. Such a theory would explain the characteristic asthenia of the disease. Some authors today seem to incline to the theory that Addison's disease is essentially a deficiency of the chromaffin tissue, i. e., adrenal medulla and accessory bodies. Some, however, regard the cortex as the structure involved. The facts justify the opinion that both cortex and medulla are involved in the deficiency. It may also, if we postulate a detoxicating function, arise as a result of intoxication from products of metabolism which the hypofunctioning adrenals fail to neutralize or remove. Autopsy findings show from 85% to 90% of cases to have adrenals affected by some structural degenerative process. The great majority show tuberculosis of the adrenals, which seem to be a common site of primary infection. The lesion is usually of the fibro-caseous type. Cirrhosis and atrophy are also common and sometimes neoplasm, chronic inflammation and syphilis are found. A small number of cases show apparently normal adrenals.

Diagnosis, Course and Prognosis

The diagnosis rests upon the recognition of the symptoms above described: The marked asthenia, inability to perform muscular work, apathy and utter listlessness, the characteristic discoloration of the skin,

the gastrointestinal, nervous and psychic symptoms. The onset is insidious, slow, and the impaired muscle efficiency is the most characteristic symptom. The discoloration of the skin may appear at almost any period of the disease.

A special diagnostic procedure which has received much criticism as to reliability is the "white line" of Sergent. This is performed by gently, and with light superficial stroking with a smooth, blunt object, outlining a square on the abdomen of the patient. The smooth end of a fountain pen is satisfactory for this purpose, and it is essential that the stroking be superficial and without pressure. The patient should be in a recumbent position. A positive reaction is evidenced by the appearance of a pale line, after ½ minute's time, which quickly becomes clear cut and white. It lasts for two or three minutes and disappears. So much criticism has been directed against this procedure that its value is much in doubt. Sergent[55] has outlined some of the objections to this test. The disease extends over a variable period of time and may last for years. The prognosis is always grave.

Treatment

Addison's disease is usually resistant to any method of treatment. Organotherapy with adrenal substance offers the greatest hope, and in the hands of numerous observers has proved far more effective than all other therapy. Epinephrin is less effective than whole gland preparations. Sajous says:[56]

> "Either the fresh gland, a glandular extract, or the dried gland, all representing the whole gland, must be used to expect beneficial results, as shown by a personal study of 120 reported cases."

Osborne says:

> "However, it seems to be a fact when the suprarenal glands are not too seriously injured that there is some improvement from feeding suprarenal extract, and naturally the whole gland must be given, the administration of epinephrin representing only a small part of the activities of the adrenals."

This represents the best opinion on the subject today. In view of the uncertain pathology, that both cortex and medulla may be involved, and of the clinical experience as well, whole gland preparations are to be preferred. The dosage should usually be small, unfavorable results having been reported from too high dosage. Sajous says:[60]

> "The essential feature in carrying out this mode of treatment is to adjust the amount administered to the needs of each case. Addison's disease being due, from my viewpoint, to inadequate oxygenation and metabolic activity, the results in turn of a deficient production of the adrenal secretion, it follows that the temperature and blood pressure indicate the degree to which the adrenals are still performing their functions. It is plain, therefore, that our aim should be to supply only just enough adrenal extractive to compensate for the deficiency of adrenal secretion produced."

One grain tablets of the desiccated substance may be used. Sajous advises three grains twice daily during meals, if the blood pressure and temperature are considerably below normal. Smaller or larger doses may be used, according to indications. Pituitary is also recommended by Sajous and Osborne. This may be administered hypodermatically.

Some favorable results of suprarenal grafting have been reported. Suprarenal therapy is in no sense a specific for Addison's disease. It represents, perhaps, the best hope available today and is certainly worthy of continued investigation.

CLINICAL TYPES

Several types may be recognized, depending upon whether the cortex or medulla is involved. Whole gland deficiency is represented by Addison's disease (see above).

Chromaffin Tissue (Adrenal Medulla)

Hyperfunction	Hypofunction
Arteriosclerosis, Vascular hypertension, Associated sclerotic nephritis, Heightened activity of sympathetic nervous system.	Pigmentation of skin and mucous membranes, Asthenia and muscle inefficiency, Vascular hypotension, Underdevelopment of sex organs, Hypoglycemia.

Adrenal Cortex

Hyperfunction	Hypofunction
Sexual precocity, Increased growth of hair, Increased muscular development or obesity, In female children—enlarged breasts, early appearance of hair on genitals, well-developed uterus and enlarged clitoris. Tendency to male type in women, with marked development of hair, menstrual abnormalities.	Lack of sexual development.

PREPARATIONS, DOSAGE AND ADMINISTRATION

Adrenal substance is used in medicine as the desiccated powder of the whole gland, cortex or medulla, and as the active chemical compound, epinephrin, extracted from the medulla. This may also be prepared synthetically. The dosage of the whole desiccated substance is from 1 to 4 grains, of the medulla 1 to 2 grains, and of the cortex 1 to 4 grains. The smaller dosage is usually preferable, if the administration is to be long continued

or if it is combined in a pluriglandular prescription with synergistic gland substances. Epinephrin is used in solutions of from 1: 20,000 to 1 : 1,000. The base, epinephrin, is itself almost insoluble and practically all preparations are solutions of the hydrochloride. It is marketed in tightly sealed bottles of 1 oz. size and in 1 c. c. ampoules. Bottles should be of dark colored glass and the preparation should not be exposed to the light. It may be used in either aqueous or oil solution.

The desiccated substance is given by oral administration. Epinephrin is given hypodermatically and applied locally. The desiccated substance should be taken after meals, as it may cause nausea on an empty stomach. Increased blood pressure, increased heart action and headache are symptoms of too high dosage.

The stronger solution (1 : 1,000, etc.) of epinephrin may be given orally or used as a local application. Epinephrin is largely destroyed in the gastrointestinal tract, but in high concentration sufficient is absorbed to give physiological effect. Epinephrin may be given in suppositories, but there appears to be little use for such a method except for local effect. Solutions of from 1 : 20,000 to 1 : 1,000 may be used hypodermatically. The stronger concentration should be diluted with sterile water. The usual dose is from ½ to 1 c. c., which may be repeated several times during the day. For oral administration, 10 drops to 2 c. c. diluted with a like amount of water of the 1 : 1,000 concentration may be given every two hours. This should be held under the tongue and absorption permitted to take place from the mouth. One c. c. ampoules of a 1 : 10,000 concentration represent the usual practice in hypodermatic administration. Locally and as a spray, solutions of 1 : 15,000 to 1 : 10,000 are generally used.

Idiosyncrasy to epinephrin is rather common. After hypodermic injections of average dose, the following may sometimes occur: psychic symptoms, apprehensive feeling, trembling, paleness, rapid and irregular heart action. The symptoms are usually not serious or lasting.

THERAPEUTICS

Addison's Disease. (See above.)

Anesthesia Epinephrin is included in solutions of most drugs injected for local anesthetic effect. By constricting the capillaries of the area, it delays absorption of the drug and permits a longer duration of effects. The dosage of such anesthetic substances may also be largely increased, as the slow, gradual absorption does not permit entrance to the organism of a quantity sufficient to produce toxic effects. Cocaine appears to be synergistic to epinephrin, so that the local effects of epinephrin with cocaine are greatly intensified. Chloroform and ether depress the function of the adrenals, and the depression following general anesthesia may be satisfactorily treated with suprarenal preparations (epinephrin).

Asthenia In all forms of asthenia adrenal therapy is of value. It is usually more effective, however, when combined with thyroid and other gland substances. In neurocirculatory asthenia this is particularly true. " While a part of the neurocirculatory asthenia of enlisted men is due to thyroid hyperactivity,

(See page 233)

part is due also to suprarenal insufficiency. Rather typical of adrenal insufficiency are cold hands and feet and bluing of the lips on the least exertion. Although it has been shown that epinephrin secretion does not seem necessary for the maintenance of normal blood pressure, it is very necessary to develop an increased blood pressure when the pressure is subnormal and the circulation insufficient." [66]

Asthma

Epinephrin is invaluable in the symptomatic treatment of bronchial asthma. It acts through relaxing the tensed bronchial muscles and by preventing the contraction of bronchial muscle from taking place. This effect takes place through the stimulation of the sympathetic nerve endings of the bronchi, which dilate the bronchioles. It is generally used for this purpose and appears to be free from any harmful effects. The relief may last for hours. The best results are obtained from hypodermic administration of from ½ to 1 c. c. epinephrin solution of a strength of from 1 : 10,000 to 1 : 1,000. It may be used as a spray. Osborne says: "The value of suprarenal, and especially of epinephrin, in asthma has now long been noted. An epinephrin tablet crushed with the teeth and allowed to absorb from the mouth, or 5 to 10 drops of an epinephrin solution of 1 part to 1,000, will usually stop an asthmatic attack." [66]

Blood Pressure—Low

Adrenal substance is commonly used in conditions attended by low blood pressure, to restore a normal arterial pressure. For this purpose, a combination of glands exerting a synergistic effect is advisable (adrenal, with thyroid, pituitary and gonads—Hormotone). The action of the adrenal substance itself is probably one of homostimulation.

> "The rise in blood pressure after the administration of epinephrin, when given on the tongue or hypodermatically, or when it is absorbed from mucous membranes other than the stomach, quickly occurs, but it does not last long. This action is not, however, the action that causes the greatest help; it is the stimulation that it causes to the suprarenal glands. A blood-pressure raising treatment that lasts such a short time could be of only momentary help; consequently, as soon as the emergency is past, after administering epinephrin hypodermatically or on the tongue (though such treatment may be repeated a few times, especially on the tongue), the greatest advantage from suprarenal treatment is obtained by giving the whole gland extracts by the mouth. When given in tablet, the tablet should be crushed and swallowed with water. The blood-pressure raising substance seems to be changed chemically in the stomach, so that it does not cause the usual rise of arterial pressure, but the rest of the gland seems to stimulate and help a depressed circulatory condition." [67]

Heart Failure

By reason of its direct action in stimulating heart action, epinephrin has found some use in restoring heart action in conditions of emergency. As its effects are of short duration, its use seems limited to the treatment of emergencies. Action has been reestablished in hearts which have stopped beating, the direct introduction

of an epinephrin solution into the heart or pericardium being resorted to. The greatest caution is necessary in such cases, as large doses are fatal, producing cardiac dilatation.

Hemorrhage—Concealed In addition to its use as a local application for the control of hemorrhage, epinephrin also has been used in pulmonary hemorrhage. Its value in this condition is much in doubt, but in view of the reported successes and the absence of other methods of treatment it may be used. The dose should be less than ½ c. c. of a 1 : 1,000 solution, administered hypodermatically and repeated every 30 minutes. Some authors, however, hold it to be valueless, and even harmful for this purpose. Wiggers has used epinephrin in intestinal hemorrhage and believes that, when the hemorrhage is large, is continuing, and is attended by low blood pressure, epinephrin should be given to cause a moderate rise in blood pressure. It may be administered hypodermatically, in a dosage of 10 c.c. of a 1 : 1,000 solution, or orally, 1 to 2 c.c. of a 1 : 1,000 solution in water. Large doses of desiccated whole adrenal substance or adrenal medulla may also be given.

Hemorrhage—Local For the control of hemorrhage from mucous membranes of the nose and throat and other sites to which it can be directly applied, epinephrin has a very wide use. As a spray or applied by means of gauze, it is very effective. Solutions of varying strength may be used. Oil solution of 1/10 per cent of the alkaloid base may be used. Aqueous solutions should be freshly prepared and of strength of from 1 : 15,000 to 1 : 5,000.

Hemorrhoids Hemorrhoids may be reduced in size and bleeding controlled by epinephrin suppositories.

Laryngitis Spraying with an oil solution of epinephrin is of value in acute laryngitis and in localized inflammations of the nose and nasopharynx. Bronchitis may be relieved if the spray is sufficiently tenuous to reach the bronchi.

Rickets Epinephrin has been found useful in the treatment of rickets[64] and osteomalacia.[65] Such a use may be regarded as a promising field for more investigation. Chabrol and Hagueneau[66] found that x-ray pictures and microphotographs of the endocrine glands of a patient with osteomalacia showed that the pituitary, thyroid and adrenals were enlarged. This is suggestive, in view of the good results of adrenal therapy and that osteomalacia is considered by some to be caused by adrenal hypofunction. The opposed influence of the adrenals to the ovary is suggested by the reported success of adrenal therapy and the known influence of ovariotomy in osteomalacia.

Salvarsan Some of the untoward effects of salvarsan administration may be avoided by oral administration of epinephrin prior to the injection; 2 c. c. of a 1 : 1,000 solution may be given one hour before and one hour after.[68]

Seasickness Epinephrin orally or hypodermatically administered has been said to be effective in the control of seasickness. It is worth trial, but such use must be considered still unproved. Sicoli[69] finds it useful combined with bromides.

Vomiting Advantage has been taken of the well known action of epinephrin in inhibiting the movements of the stomach and intestine to relieve vomiting and the vomiting of pregnancy. The results have been good. One c. c. of the 1 : 1000 solution may be given and repeated if required.

Contraindications to Epinephrin

High blood pressure.
Myocardial disease.
Cardiac dilatation.
Aneurysm.
Arteriosclerosis.

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PART II

CHAPTER IV

THE PITUITARY BODY

The term "hypophysis" is frequently used, but, as stated by Bell, should refer to the epithelial portion of the pituitary only, the pars anterior and pars intermedia. It is very common, however, to find "hypophysis" used as a synonym for the entire pituitary body, while in the U. S. Pharmacopœia "Hypophysis Sicca" and "Liquor Hypophysis" refer to posterior lobe preparations.

ANATOMY

The pituitary body rests in the sella turcica, a cup-shaped depression in the sphenoid bone at the base of the brain. The average weight is from 60 to 70 centigrams. It is made up of two major parts, the anterior and posterior lobes, distinct morphologically and in embryological origin; and is suspended from the floor of the third ventricle by the infundibulum, a hollow stalk which widens to form the posterior lobe or pars nervosa. Two smaller structures, the pars intermedia and the pars tuberalis, are included in the pituitary body. The anterior (pars glandularis) lobe is derived from the buccal ectoderm (Rathke's pouch), is glandular in structure and partially surrounds the posterior lobe. Embryologically this part develops as a tubular organ (sac) and in the adult the two parts are separated by a cleft, the intraglandular cleft, which is a survival of its original tubular structure. Some of the epithelial cells of the anterior lobe (the posterior wall of the tube) become separated from the main body, and, as a thin layer, surround the body and neck of the pars nervosa, separating it from the intraglandular cleft. This layer of epithelial cells is the "Pars intermedia," and is adherent to the posterior lobe into which some of its epithelial cells infiltrate. It is separated from the anterior part by the cleft. The pars tuberalis appears to be a separate structure and extends along the stalk of the infundibulum. It is epithelial and is believed to have an embryological origin separate from the other structures. The anterior part is composed of masses of epithelial cells, irregularly arranged in column formation with occasional crude acinus formation. There are three main types of these cells, those not taking stain (chromophobe), granular cells taking stain (chromaphil), some taking an acid stain (most numerous) and some taking basic stains.

The posterior part arises from the nervous tissue of the floor of the third ventricle, and is composed chiefly of the neuroglia cells. The anterior part is very vascular; the posterior and pars intermedia much less so.

Histologically there may be demonstrated hyalin, colloid or granular masses between the neuroglia cells. These are absent from nervous tissue elsewhere and are believed to constitute the internal secretion of the posterior part. Collections of these hyalin bodies have been shown in the infundibulum, passing into the third ventricle. Herring [1] states that these masses of cells have their origin in the pars intermedia which infiltrates the posterior part. These cells degenerate and are finally discharged into the third ventricle. The active pressor principle of the posterior part may be detected in the cerebro-spinal fluid, a fact which has been quoted as evidence of this mode of entrance of the active principle of the posterior part. Bell, however, does not believe that this represents the mechanism by which the secretion of the posterior part and pars intermedia as a whole is taken up by the organism. He believes that the secretion passes, in part at least, into the general circulation by discharge into the blood stream. The secretion of the anterior part is probably carried away in the blood channels.

Accessory pituitaries are rarely found and may result from embryological abnormality and occupy a position in or near the sella turcica. As a consequence of the embryological development, in which a pouch from the buccal entoderm migrates into the cranium and subsequently becomes cut off by the development of the bony structure of the sphenoid, a canal sometimes persists in this bone—the canalis craniopharyngeus. The pharyngeal hypophysis is also a remnant of the origin in the pharynx and is a very small structure.

Blood Supply

The blood supply is derived from the internal carotids and from the circle of Willis. The vessels arise from about 20 small arterioles that reach the pituitary from the circle of Willis and pass along the infundibulum into the gland. The capillaries are very profuse in the anterior part and pass as sinus-like vessels between the columns of epithelial cells. The venous return is through the circular sinus.

Nerves

The nerve supply is not entirely worked out, but appears to be limited to sympathetic fibers arising in the carotid plexus and distributed to the anterior lobe. Such fibers have been shown by Dandy and Goetsch.[2]

PHYSIOLOGY

In addition to the study of the results of the pathological processes affecting the tissues of internal secretion, the function of the pituitary has been investigated by two general procedures: extirpation and study of the effects of the administration of extracts. Many positive effects have been learned from injection of extracts of the posterior lobe in contradistinction to those of the anterior, which have largely given negative results. The anterior lobe without doubt furnishes some internal secretion which exerts a profound influence on growth, development and nutrition,

particularly of the skeleton. It also probably has some specific effect on sexual development; but the manner in which it acts is not demonstrable by injection methods. During pregnancy the anterior lobe undergoes marked hypertrophy. The posterior lobe may in normal physiology give rise to a substance which regulates the reactivity of unstriped muscle fiber: such a principle extracted from the pituitary may be demonstrated on muscle preparations, but its effect in the body in a similar manner has not been proved. It doubtless also plays an important though undetermined part in general metabolism, and probably has a specific function in carbohydrate metabolism. It may also exercise an effect in regulating diuresis.

Posterior Lobe

As a result of injection experiments with extracts of the posterior lobe or of the whole lobe, the following effects have been ascertained.

Effects on the Vascular System

Injections of the posterior lobe are followed by marked and characteristic effects in the circulatory system—a great rise in blood pressure, contraction of blood vessels and slowing of the heart. The rise in blood pressure is more prolonged than that produced by epinephrin, and the constricting effect on capillaries is evident in both the coronary and pulmonary vessels. The effect may last for one-half hour. Howell [3] showed that these effects were due to the principle in the posterior lobe alone. The specific mode of action in the production of these vascular effects is unknown and may be through the central nervous system, the peripheral nerve endings, or a direct action on the heart muscle. It is characteristic of these extracts that a second injection given a short time subsequent to the first gives almost no effect and that there may even be a slight fall in blood pressure. Schäfer assumes from this that there may be a second principle in the extract of the posterior pituitary which is antagonistic to the first and should be classed as a "chalone" (an internal secretion exerting a hindering or depressing effect). It has been stated [4] that this lowering of the pressure is due to a depressor substance found in practically all organic substances; but this is not generally accepted. Führer [5] believes that there are four active principles in the posterior lobe which influence the organs of circulation and of respiration, kidneys, intestines and uterus. The presence of a depressor substance in solutions made from the posterior lobe seems fairly well established. Such a substance has been isolated and is probably present in all such extracts, but is overbalanced by the predominating effects of the pressor principle. These active principles of the posterior pituitary are unknown. Histamin has been isolated, but is not regarded as the characteristic pressor principle. There are probably at least three, a pressor, a relaxing and a uterine contracting. The extracts used in therapeutics are assayed for the latter principle only, but always contain a mixture of all. With the rise in blood pressure there is an attendant slowing of the heart, neither of which is as marked as that produced by adrenalin. Pituitary stimulates the heart even after the vagi have been cut or paralyzed by atropine. The slowing, however, persists. Wiggers [6] holds that the slowing of the heart is a result of stimulation of

the cardio inhibitory center. The rise in blood pressure, due to constriction of capillaries, might produce such an effect. By some the actual strength of the heart beat and ventricular efficiency are said to be diminished. Repeated injections are stated to result in hypertrophy of the heart.

Posterior lobe extracts apparently give rise to a stimulating effect upon plain unstriped muscle all over the body—intestine, bladder, uterus, stomach and spleen all show contractions. It is to be noted that posterior lobe usually gives contractions in distinction to adrenalin, which may give either contraction or relaxation, depending upon the character of the autonomic nerve filament supplying the plain muscle. The internal secretion of the posterior pituitary probably acts directly on the muscle cell (Howell). Magnus and Schäfer showed that on the smooth muscle of the spleen the posterior lobe extract causes contractions.[7]

Action on the Kidneys

Magnus and Schäfer also demonstrated that such extracts caused diuresis and that the vessels of the kidney are dilated by these extracts, although elsewhere there is arterial contraction. Stoland and Korb[8] found that after injection of solution of post-pituitary the volume, total nitrogen, urea and ammonia were increased as much as 50% and the total nitrogen and urea of the blood were lowered about 40%, while on the day following the injection, although the volume was about normal, the total nitrogen, urea and ammonia were decreased as much as 20%. They conclude from their experiments as follows: "The above results seem to show conclusively that pituitrin acts as a stimulant to the kidney in that it produces such a marked secretion of urine that the nitrogenous content of the blood falls far below normal." This work may be taken as evidence refuting the claims of some of the presence of an anti-diuretic effect of posterior pituitary (Motzfeldt, Bab and others). T. Addis, G. D. Barnett and A. E. Shevky[9] found diminished urea excreting activity of the kidney after injection of solution of post-pituitary. The diuresis was thought to be probably due to direct action on the kidney cells,[10] for it takes place after repeated injection when vasoconstriction fails to take place and when kidney vessel dilatation is absent. This opinion has been supported by Hoskins and Means[11] and denied by Houghton and Merrill[12] and King and Stoland[13] and others. The investigations of Knowlton and Silverman, however,[14] do not give any evidence of oxygen consumption by the kidneys. They conclude, therefore, as follows:

> "1. The oxygen consumption by the kidneys is not increased during the diuresis induced by pituitary extracts.
>
> "2. Using the oxygen consumption as the criterion, there is no evidence that pituitary extract stimulates the renal cells.
>
> "3. Throughout our experiments increased blood flow through the kidney was an invariable accompaniment of pituitary diuresis.
>
> "4. From the evidence at hand, it seems possible to explain the diuretic action of pituitary extract entirely on the basis of the vascular changes and increased filtration pressure obtaining in the kidney."

In some degree, however, we may believe diuresis to be due to increased blood supply as a result of general arterial contraction and concomitant

dilatation of the arteries of the kidney, and also to some direct stimulation of renal cells.

Action on the Uterus

The action on the uterus is very pronounced, and appears to be specific. Bell states that his experiments on rabbits showed that there was no reaction in the non-pregnant uterus, but that violent contractions occurred in the pregnant uterus. Dale,[15] however, states that the non-pregnant uterus will show a positive response, and it is generally accepted that pituitary stimulates pregnant or non-pregnant uterine muscle. The rabbit uterus, perhaps, shows some difference in this respect from other animals. This action is used in the method of standardizing posterior pituitary preparations.[16] Lieb's work[17] on the human uterus shows that both the pregnant and non-pregnant uterus contracts after stimulation by pituitary. Dale believes that the extract acts in increasing the sensitivity of the uterine muscle to normal stimuli, rather than directly exciting it. This idea is also held by Bell, who states, "I came to the conclusion that infundibulin not only augments contractions in the expulsively contracting or potentially contracting uterus, but also sensitizes the non-contracting musculature which thereafter responds readily to mechanical stimuli." Extracts of anterior part have no such action, and it has been shown[18] that extracts of the pars tuberalis are very inferior even to those of the pars intermedia in their effects on contraction of the uterus. The effect of extracts on the intestine is to raise the tone. Contractions are usually produced.

Galactagogue Effects

The interpretation of the effects of the posterior pituitary extracts on the mammary gland is not clear. The increase in volume of milk is believed by Schäfer to be due to contraction of the plain muscular tissue around the alveoli. He says,[19] "Apart from the pouring out of the contents of the alveoli—which, when the gland is intact, shows itself as a tendency of the alveoli to empty themselves towards the nipple—the pituitary galactagogue has little or no effect on the total production of milk." Hammond,[20] however, believes that the effect is a result of direct stimulation of the secreting epithelial cells of the mammæ. It is probable that there may be some small increase in milk production as a result of the injection, but that the main effect is that due to contraction of the muscle fibers of the mammary glands.

Effects on Carbohydrate Metabolism

Injections of solution of post-pituitary cause a lowering of carbohydrate tolerance, and glycosuria results.[21, 22] This action has been accounted for by the action of a hormone, presumably upon the liver cells. "We assume that the spontaneous glycosuria represents a hyperglycemia from the discharge of stored glycogen which has been set free by the introduction into the circulation of the posterior lobe secretion."[22] Keeton and Becht,[23] in experiments carefully conducted to exclude any factor of lowered renal threshold or effects of anesthesia, found that electrical stimulation of the pituitary in dogs results in an increase in the reducing substances in the blood. Stimulation of the contiguous areas of the brain does not give this effect. These investigators believe that their work is in opposition to a theory of hormone liberation acting on liver and

muscle cells in causing these effects, and suggest a nervous mechanism—a subject which they state needs investigation. Shamoff [24] corroborated these results. After stimulation of the cervical sympathetic he found:

"1. There usually occurs a characteristic hemodynamic response;

"2. As was observed by Weed, Cushing and Jacobsen, as well as by myself, glycosuria is provoked; and finally

"3. A polyuria, resembling that produced by intravenous injection of pituitary body extracts, frequently occurs."

In a subsequent study [25] Keeton and Becht duplicate their former results in causing hyperglycemia by stimulation of the hypophysis, but find that it does not take place after transection of the cord at the level of the second thoracic vertebra and section of the splanchnic. They reassert their opinion that the effect is through a nervous mechanism mediated through the splanchic nerves passing to their termination in the adrenals and liver, and state, "The physiological rôle played by the hypophysis in carbohydrate metabolism does not deal with transformation of glycogen into sugar, but more probably with the utilization of the sugar by the organism." They do not wholly dismiss the possibility of hormone action, but state that if present it must have a central action. As a result of most of the evidence, it is held that the pituitary furnishes a hormone or exerts a nervous action which has a function in sugar metabolism. The effects on metabolism in general are not well understood, but the experimental work reported by various investigators indicates some general effect on metabolism. In experiments conducted to ascertain the effects of oral administration on changes induced in the amounts of total nitrogen, non-protein nitrogen, sugar and alkaline reserve of the blood, Hammett, Patten and Suitsu [26] found the only consistent change to be an increase of the uric acid of the blood. McKinlay [27] found that the basal metabolism of normal persons is quite constantly increased following injection of pituitary extract.

Anterior Lobe

The known facts of the functions of the anterior lobe have been ascertained through the results of extirpations (see page 121), feeding experiments and clinical pathology. The hormone produced by the anterior pituitary is indispensable to life and is directly related to the growth and development of the animal, particularly of the skeleton and sexual organs. The active principle or hormone is unknown, although the substance "tethelin" isolated by Brailsford Robertson [28] appears to have characteristic growth producing effects. This substance may be obtained from the anterior pituitary by Robertson's process, and appears to be of constant composition. Nothing is known of its chemical constitution or as to whether it is a mixture of several compounds. It appears to give the same results in growth as whole anterior pituitary. Applied locally it has been found to stimulate cell growth and granulation tissue in indolent ulcers.

Feeding Experiments

Most of the results of the earlier feeding experiments with pituitary substance were discordant. The factors which contributed to this are now fairly well known and were (1) difference in species of animals used; (2) use of whole pituitary (mixture of anterior and posterior lobes); and (3) failure to take into account the growth period or stage of development of the experimental animal. Robertson and others have shown that the growth effects of administered pituitary may be very largely affected by the age of the animal. Growth may even be accelerated or delayed, depending upon the age.

Whole gland feeding is attended by inconstant results. Growth is usually retarded, although the growth of the sexual organs is stimulated. These effects in stimulation of growth of sexual organs may be very pronounced, and include precocious development, hypertrophy and increased functional activity, and are manifest in both male and female animals. The effects upon metabolism are not well worked out, but there appears to be increased excretion of nitrogen and phosphorus and retention of calcium. The results of various observers are not concordant.

Posterior Lobe Feeding

Feeding experiments with the posterior lobe show inhibition of growth instead of acceleration. This applies to the effects on the sexual system, as well as to growth in general. Large quantities of ingested pituitary substance give rise to toxic symptoms. The action of extracts of pars intermedia is somewhat similar to that of the posterior lobe. It has a uterine contracting principle, but in only $\frac{1}{2}$ to $\frac{1}{5}$ the quantity of the posterior lobe; galactagogue effect, a pressor effect, but no diuretic effects. Herring [29] concludes that the substances in the pars intermedia represent the precursor or partially formed substances of the posterior lobe (see above). It is stated by some (Vincent) that it is probable that the effects of extirpation on the genital organs, as well as the polyuria and disturbed carbohydrate metabolism, are the result of deficiency of the pars intermedia.

Anterior Lobe Feeding

Feeding of the anterior lobe in various species of animals, including mammals, results in definite stimulation of growth and development in general and an apparently selective stimulation of the sex organs, leading to precocious sexual development, early development of the secondary sex characteristics, libido and functional capacity. These conclusions are now generally accepted and an analysis of the results of most of the recorded experiments, allowing for known sources of error, tends to support them (experiments of Goetsch, Marinus, Exner, Cushing, Hoskins, Uhlenhuth, and others). The effects on metabolism are not clear. Blood pressure is lowered in some degree by the administration of anterior pituitary. The work of some investigators (Hamburger) shows a very decided fall in the arterial pressure. The loss of weight observed in whole pituitary feeding does not occur, nor other symptoms suggesting a toxic effect, which are found in feeding large amounts of whole pituitary. The results are, moreover, apparently not due to the pars tuberalis, for in feeding experiments upon 100 white rats Marinus [30] found that, although the group fed upon

anterior pituitary "exhibited increased growth rate, accompanied by a more rapid development of the reproductive system, evidenced by gross and microscopical hypertrophy of the organs and by the earlier birth of young," the group fed upon pars tuberalis showed no change in the sexual development as compared with that of the control group and the growth rate was slightly slower.

Effects of Extirpation

Experiments by Paulesco, Cushing, Biedl, Bell and others in the extirpation of the hypophysis in animals are in practical agreement that removal is followed rapidly by death. Upon removal of the posterior lobe alone, the animals live indefinitely without symptoms, but when removal of the anterior lobe alone is performed, although the animals may live for weeks, death always follows, and there is shown upon autopsy marked deposit of fat on the omentum and in the retroperitoneal space. There is also pronounced atrophy of the testicles and ovaries. Partial extirpation of the anterior lobe is not fatal, but may be attended by atrophy of the sexual organs, deposit of fat, dullness, defects of bone growth and lack of sexual power (artificial dystrophia adiposo-genitalis). It is evident that "the anterior hypophyseal lobe represents the vital portion of the organ, the complete extirpation of which is followed by death; its partial extirpation by disturbances of growth and metabolism and by derangement of the activity of the sexual organs." (Biedl.) It is also evident from the experiments of Paulesco that there is some vital function bound up in the peduncle, for even when the hypophysis is left *in situ* and the peduncle severed the animal dies as promptly as when the hypophysis is completely removed. Bell, however, fails to verify the production of dystrophia adiposo-genitalis following the partial extirpation or injury of the anterior lobe, but finds that it does follow compression or separation of the stalk of the infundibulum. He concludes that dystrophia adiposo-genitalis is caused by insufficiency of the anterior part and that experimentally the most certain way of accomplishing this is by cutting off the blood supply by compressing or severing the infundibulum. Camus and Roussy [81] are among the few who dissent from the general conclusions above. As a result of total or partial extirpation of the pituitary in 122 dogs, and 27 cats, they conclude that the pituitary is not necessary to life. They attribute death, occurring after hypophysectomy, to shock, hemorrhage, meningitis or lesion at the base of the brain and not to pituitary insufficiency. It is known that injury to areas of the brain near the pituitary will result in polyuria and glycosuria, and the rôle of the brain centers in the result of hypophysectomy demands more study. P. Bailey and F. Bremer found [82] that even minute lesions of the para-infundibular region of the hypothalamus cause polyuria. They state that there is no evidence that the lesion acts through the pituitary. The general conclusions first stated above, however, are held by the majority of physiologists.

EXCESSIVE HYPOPHYSEAL FUNCTION

ACROMEGALY

Pierre Marie (1886) first recognized and described the relationship existing between the condition of acromegaly and pathological changes in the pituitary gland. Minkowski in 1887 also described the condition and discussed its connection with the pituitary. It was at first assumed that such changes were attended by decrease or loss of function of the pituitary; a view not now held. It is now generally believed that the characteristic and fundamental changes occurring in the clinical picture of acromegaly are due directly to an increased functional activity of the glandular portion of the hypophysis. By many adenoma of the pituitary is believed to be causative. It is held by some, however, to be due to pituitary dysfunction. Acromegaly is a disease presenting well-marked signs and symptoms, making a clinical picture that in even moderately advanced cases is unmistakable. Among the early symptoms are headache, psychic disturbance, irritability, thirst, polyuria and disturbed vision. Visual abnormalities are particularly common—blurring, narrowing of the visual field, etc. In men impotence and in women sterility are common. Dullness, approaching stupor, is frequent. It is characterized by rather slow enlargement of the bones of the body, particularly those of the hands, feet, lower jaw, etc. The soft parts may also show changes, and the tongue and skin are enlarged and thickened. The whole skeleton may exhibit changes. The pituitary is enlarged and, as this hypertrophy becomes marked, the sella turcica is distended and the clinoid processes widened and even obliterated. Pressure symptoms result and headache of a characteristic variety is common.[33] In females there may be abnormalities of hair distribution, the eyebrows may become thickened and bushy, there may be excessive growth of hair on the upper and lower lips and on the chin. Excessive hairy growth is found, however, in both sexes and is usually marked and characteristic. Excessive growth may occur in either sex and involves the head and tongue, and extremities as well. The abnormalities of the bony parts are the most conspicuous and characteristic of the physical signs. The sutures and fontanelles may ossify at a very early age. The distortion of features and deformation of bones of the head and face are characteristic and usually progressive. The distortion of the features is not wholly due to the alteration in the bones, but to involvement of the soft parts as well. The tongue may be enormously thickened and the mucosa of the mouth and pharynx hypertrophied and thickened. The larynx may show marked involvement.[34] The nose may be greatly enlarged. The zygoma protrudes and enlarges; the eyebrows become prominent. The teeth may be widely separated and particularly the spacing between the incisors may be widened. The hands and fingers are greatly increased in size and the fingers become club-shaped. The feet are also enlarged. There is usually some arteriosclerosis and, frequently, cardiac hypertrophy, with subsequent degenerative changes and symptoms of insufficiency. During the course of the disease, kyphosis and lordosis may develop. There is marked broadening and thickening of the areas of insertion of the muscles of the ribs. Osteophytes are of frequent occurrence. Changes are most characteristic at the epiphyses of the long

bones, which are thickened and enlarged. The lower jaw is especially apt to show changes and is enlarged and protruding. The clubbing of the fingers is attended by thickening of the epiphyses of the phalanges. There is usually in the early stages an increase in development of the secondary sex characteristics. The growth of the hair, as noted above, may be greatly increased and there is hypertrophy of the external genitalia. There is increased activity of the interstitial glands and in girls there is a development of the masculine type. Usually, as the disease progresses, there is loss of the functional activity of the sex glands. Physical strength may remain normal, but there is usually a progressive increase of fatigability. Rheumatoid pains in the joints are common.

In the clinical picture of acromegaly there are frequently symptoms not directly referable to the hypophysis. These are due to other glands of internal secretion which sooner or later become involved. The thyroid gland is almost invariably at fault and in sufficient degree to affect the symptomatology. Frequently, in the earlier stages, there is evidence of hyperthyroidism—later in acromegaly, evidences of myxedema may appear. The sex organs are commonly involved. In the first stages they tend to undergo stimulation and hypertrophy with accentuation of secondary sex characteristics and increase in sexual activity. This is followed by a marked regression and impotence, and amenorrhea and sterility are the rule. Tandler and Gross [35] believed the affection of the gonads to be the primary lesion and the hypophyseal involvement secondary. There is frequent association with glycosuria and diabetes mellitus. The suprarenal cortex frequently shows hyperplastic changes. Symptoms referable to pressure on contiguous areas of the brain are also common—optic atrophy, impaired vision, etc. Acromegaly is more frequent in women than in men, and between the ages of 20 and 40. According to Bell, it is distinctly a disease of the reproductive period, and is most frequent just following puberty. The duration is long—over a period of years. It is progressive and usually fatal. The onset is gradual. Sugar tolerance is lowered and glycosuria may develop.

Treatment

Surgical treatment has been successful. The operation is grave, however, although the operative procedure is well developed. Administration of pituitary substance is usually unavailing and may result in aggravating the condition. Ovarian substance has been successful in the practice of some and should be worthy of trial in cases occurring in females. Treatment with x-ray has also met with considerable success.

GIANTISM—GIGANTISM

The subject of giantism and acromegaly are closely associated in the literature. It is not uncommon to find the subject dismissed with the statement that the etiologic conditions are the same; giantism resulting if the process develops early and before the ossification of the epiphyses, and acromegaly if the process occurs later in adult life. While there are undoubtedly cases of giantism in which the underlying cause is not abnormal

pituitary function, it is probable that the greater number of giants have been acromegalic (the Brissaud-Meige type). Giantism may occur also as a pure macrosomia, in which the large size is simply normal for the given individual. Falta also describes some cases of giantism which are probably not of either type—the eunuchoid giantism. He states that in the majority of cases of giantism the eunuchoid signs are prominent, and does not believe that the increased functional activity of the hypophysis is, unaided, sufficient to cause giantism. "We must assume, in addition to it, a potential tendency to growth that may be either proportionate (normal giants) or, as it is mostly disproportionate, partly through an insufficiency of the interstitial glands and probably also through many other factors. It would seem that, in addition to the hypophysis, all the ductless glands are involved in a predominant manner in the hyperplasia."

Bassoe[36] states that the majority of giants described in the last 20 years can be classified under one of the following groups:

1. Gigantism with infantilism,
2. Gigantism with acromegaly,
3. Gigantism with infantilism and acromegaly.

This classification directs attention to the gonads as well as the hypophysis. There would appear to be an involvement of other endocrine glands, as well as the hypophysis, in giantism, with characteristic predominance of one or the other in individual cases.

HYPOPHYSEAL INSUFFICIENCY

Hypopituitarism, Dystrophia Adiposo-Genitalis, Froelich's Dystrophy, Hypophyseal Dystrophy

In most respects this condition is quite the antitype of acromegaly. It is generally considered today that it is due to loss or impairment of function of the hypophysis. Bell regards the condition of adiposity with genital atrophy as due to disturbance of function of the whole pituitary, certain signs and symptoms being referable to the anterior and others to the posterior lobe. It was described in 1901 by Froelich and is characterized by obesity, in which the accumulations of fat are usually localized on the abdomen below the waist line, and around the hips, buttocks and the mammæ. It should be stated, however, that obesity is absent in some cases. There is usually a failure of development of the genitals and the secondary sex characteristics, due to failure of development or atrophy of the interstitial glands. If genital development has taken place, there is atrophy and degenerative change. Impotence is common and there is languor and general physiologic weakness. In females, menstruation does not take place, sexual desire is absent, and amenorrhea and sterility are common. The appearance of the hands is characteristic, with long, tapering fingers. The skin is smooth, delicate and of fine texture and typical of youth. There is scanty growth of hair. In the male there may be feminine distribution of pubic hair, and in the female a tendency to a male type of distribution. In the male there is a general tendency to the feminine type, with a feminine type of skeleton, small hands and feet, delicate skin, etc. There is a lowering of all metab-

olism (16 to 18%—Plummer), with subnormal temperature and blood pressure. Carbohydrate tolerance is increased in most marked degree. There is lowered basal metabolism, carbon dioxide exchange, and oxygen consumption. Bell states that the sugar tolerance may be reduced and the blood pressure raised by injections of the extracts of the posterior lobe. Polyuria is frequent. There is drowsiness and general apathy, and in children mental retardation may be conspicuous. There is a striking similarity between the symptoms of pituitary ablation and dystrophia adiposo-genitalis.

Many differences in the clinical picture arise as a consequence of the varying effects of the age and sex of the individual. If the condition arises before puberty, the lack of growth principle of the anterior pituitary gives an element of general stunted growth added to the other symptoms. Bell classifies hypopituitarism before puberty as resulting in three distinct conditions:

"(a) Infantilism, somatic and sexual without adiposity (Lorain type).

"(b) Stunted growth with sexual infantilism and adiposity.

"(c) Overgrowth with some adiposity and genital inactivity."

The second (b) is the Brissaud type, and the third group (c) is the Neurath-Cushing type. The following description of the first two types is Hewlett's taken from Beck's article on Froelich's Syndrome:[37]

> "Brissaud Type: Round, chubby face, lips projecting and plump, small nose, smooth face, fine clear skin, fine hair, eyebrows and eyelashes scant, eyes prominent, large round cheeks, infantile face and head, skeleton under-developed, neck short and chubby, body long and cylindrical, abdomen prominent, limbs round and large, layer of fat over the whole body, infantile pelvis, lumbar lordosis, rudimentary sexual organs, no hair except on head, high-pitched voice, thyroid small, mind slow, retardation of ossification, absence or retardation of second dentition."
>
> "The Lorain type[38] has been described as follows: 'Small stature, delicately formed, slender skeleton, skin soft and pale, large shoulders, lower extremities long and slender, trunk relatively small, infantile sternum and pelvis, epiphyses normally united, no fat, abdomen normal, finely chiseled face, voice high, neck long, genital atrophy, absence of or slight secondary sexual characteristics.'"

When the condition arises after puberty or in adult life, the growth disturbance tends to be less noticeable or absent, and the symptoms and signs are as described in the preceding paragraph. The female sex is predominantly affected, and the usual age is from 25 to 35 years. Bell states that mild forms of the condition are "undoubtedly much commoner than is generally supposed."

Other endocrine glands are usually involved in Froelich's dystrophy. "Many of the symptoms of dystrophy adiposo-genitalis are dependent upon the close interrelationship between the function of the pituitary and other ductless glands."[39] Those particularly important in this connection are the thyroid and sex glands.

Treatment

"Most of the symptoms of dystrophia adiposo-genitalis, unless due to a progressive neoplastic growth, are frequently favorably influenced by the administration of the hormones of the pituitary, thyroid and the gonads. The thyroid hormone is equally as important as, if not more so than, the pituitary. The ovarian and testicular have the least therapeutic effect." [40]

In a description of treatment of a well-marked case, Beck says: [41]

"On the basis of a pluriglandular syndrome, hormotone, which contains the substance of the three glands involved, was prescribed. Four tablets, with the addition of two grains of thyroid, were given daily. The results were very striking. The patient was speedily restored to normal mental and bodily vigor and was able to perform her usual domestic duties without the least fatigue; but the most remarkable effect of treatment was upon the fat dystrophy, the so-called dystrophia adiposo-genitalis, as evidenced by a rapid diminution in the circumference of the hips and abdomen.

"This rapid diminution necessitated her to resort to the free use of safety pins to keep her clothes adjusted, and in the course of two months she had to have her clothing entirely refitted, although she had just purchased new apparel before she undertook treatment. At my request she procured the measurements as recorded by her seamstress, which are as follows:

"March 1. Two weeks before treatment was begun: waist 30 inches, hips 43 inches.

"May 8. After eight weeks' treatment: waist 26 inches, hips 36½ inches.

"May 31. After eleven weeks' treatment: waist 25 inches, hips 35½ inches, a decrease of 5 inches in circumference at the waist and 7½ inches at the hips, with the loss of only one pound in weight.

"Thyroid was discontinued on June 14, but she continued to take four hormotone tablets daily until July 15, after which glandular therapy was discontinued. Since then, a period of two years, she has had no return of symptoms and retained her normal figure."

Osborne says: [42]

"The administration of anterior pituitary has its greatest value in dystrophy adiposo-genitalis, but such treatment is more successful if combined with appropriate thyroid treatment, and probably it is well in females to add ovarian extracts and in males testicular extracts to the treatment."

Hormotone admirably meets the requirements of treatment of this condition and, as suggested by Beck, may be supplemented by additional thyroid dosage, if indicated; from 1 to 2 tablets t. i. d. are usually sufficient;

and the thyroid supplementary dosage need not exceed 3 grains daily. Diet, regulated exercise, habits of life and restriction of fats and carbohydrates are useful. This treatment is also indicated in the minor grades of hypopituitarism, which are undoubtedly very common.

CLINICAL TYPES

In addition to the well-marked syndromes of pituitary origin described above, it is of value to group the several physical signs and syndromes referable to the pituitary for the purpose of forming a general clinical type picture which will aid in the recognition of pituitary malfunction in patients, in whom well marked or advanced disease processes have not taken place.

HYPERPITUITARISM	HYPOPITUITARISM
Greatly thickened nose.	Adiposity.
Prominence of superciliary ridges.	Small, atrophied sex organs.
Tendency to increased tufting of terminal phalanges.	Fat pads around the malleoli.
Coarse, heavy overhanging eyebrows and tendency to excessive growth of hair.	Increased development of the mammary glands.
Protruding thick lips and enlarged tongue.	Deposits of fat around the buttocks and the neck.
Overgrowth of bony structure (giantism before puberty, bone deformities after).	Alabaster-like skin.
Widely spaced teeth.	Amenorrhea.
Enlarged sella turcica.	Slow pulse.
Hypertrophied, thickened, wrinkled skin.	Sluggish mentality.
Hypertrophied nails.	Short stature and failure of development.
Short, square hands.	Lowered basal metabolism.
Diminished carbohydrate tolerance.	Increased carbohydrate tolerance.
Impaired vision.	Childlike voice.
Amenorrhea.	Fatigability.
Headache and dull mentality.	Sterility.
Increased basal metabolism.	Irregular menstruation.
	Subnormal temperature.
	Polyuria.
	Lack of hair growth.
	Infantile uterus.

PREPARATIONS, DOSAGE AND ADMINISTRATION

Pituitary preparations are administered in the form of desiccated gland substance by mouth, and hypodermatically in the form of extracts of the posterior part. Desiccated preparations of the whole gland are prepared from the pituitary of the ox and include anterior and posterior lobe together with the infundibulum. The glands of healthy food animals are used and desiccation is effected *in vacuo* at a low temperature. The desiccated posterior lobe is official in the Pharmacopœia as "Hypophysis Sicca," and the extract is official as "Liquor Hypophysis." Liquor Hypophysis is

a standardized preparation tested as directed by the United States Hygienic Laboratory. Desiccated anterior lobe preparations are also used. Post-pituitary may be given in a dosage of from 1/10 to ½ gr. repeated several times daily. Anterior pituitary is given in 1 or 2 grain doses, which may be repeated. Whole pituitary is given in 1 to 2 grain doses. Anterior, posterior or whole pituitary may, if indications warrant, be given in much larger dosage, however. Bell states that as much as 100 grains have been given three times a day. Solution of post-pituitary for obstetrical use is prepared in ½ and 1 c. c. ampoules. Double strength solution for surgical use is prepared in 1 c. c. ampoules. Practically all commercial pituitary solutions (for obstetrical use) are from 2½ to 3 times the U. S. Pharmacopœia standard. The solution for surgical use is from 5 to 6 times the Pharmacopœia strength.

The preparations selected are dependent upon the case and the character of action desired. Intravenous and intramuscular injections are indicated for immediate effect in surgical and obstetrical practice. For medical treatment extending over long periods of time, however, oral administration is the method of choice. For such purposes, Dalché [48] states that he has abandoned subcutaneous and, especially, intravenous injections of hypophysis, restricting himself to oral administration. "When it is a question of prolonged medication, as, for instance, in a case of fibroma, or intermenstrual dysmenorrhea, or virginal metrorrhagia, which requires hypophyseal medication for weeks and months, regular daily injection is practically impossible." Sub-lingual administration, either solution, powder or tablets, seems to eliminate the dangers of personal idiosyncrasy, and to be indicated wherever the stimulation of smooth muscle is desired.

THERAPEUTICS

Pituitary therapy has a well-established place in medical practice. In some of its uses it has largely and probably permanently replaced the older inorganic and botanical preparations. The general indications for pituitary therapy are given by Bell:

"A. For pressor effects on:
- "1. The circulatory system.
- "2. The uterus.
- "3. The alimentary tract.
- "4. The urinary system.
- "5. The spleen.

"B. For supplementary effects.
"C. For antagonistic and metabolic effects."

Practically all the uses of the pituitary extracts hereafter described fall under one or more of these headings.

Pituitary preparations are particularly valuable in the field of gynecology.

Amenorrhea In the treatment of amenorrhea, when ovarian therapy has failed, pituitary treatment may be effective in restoring menstruation.[88] The advisable treatment in the beginning, however, for these cases is a combined Thyro-Pituitary-Gonad formula

(see Hormotone in Amenorrhea, page 172). In the amenorrhea of pituitary origin, such as occurs in acromegaly for example, radiation of the hypophysis has been found of value in re-establishing the menstruation.[54] Graves says:[55]

> "The loss of libido and potentia in the male, and amenorrhea and sterility in the female, which are characteristic of hypophyseal disease, are, as we have seen, referable to disturbances of the anterior lobe, while the accumulation of fat and metabolic irregularities are the result of defects in the posterior lobe. Cushing and his school, therefore, recommended for the treatment of these cases extracts made from both lobes of the gland. In gynecologic practice extracts of the whole gland are indicated in menstrual disorders that are essentially the result of pituitary deficiency, in which cases ovarian therapy may be used in combination."

Asthma Pituitary extract has been recommended in asthma and is said to be slower in its action than epinephrin, but more lasting, and to alleviate not only the immediate spasm, but to lessen recurring attacks. Combinations of the two have been used advantageously.

Bladder Retention In the retention of urine and partial paralysis following operations, injection of pituitary solution has been found of value. It is stated by Osborne to be of value, both by oral and hypodermatic administration, in adults and in children, in incontinence of the urine and in nocturnal incontinence. Serdinkoff[51] reports remarkable efficacy of pituitary injection in retention of urine from paresis of the bladder.

Diabetes Insipidus Pituitary therapy in the control of the polyuria of diabetes has proved of distinct value. Barker[49] reports good results in the treatment of a case, probably due to involvement of the hypophysis, thyroid, interrenal system and gonads. Subcutaneous injections of the posterior lobe and pars intermedia were used. Osborne[50] states that "in diabetes insipidus, which seems so frequently due to hypophysis disturbance, hypodermatic injections of posterior lobe extracts often act almost as a specific, causing the output of urine to be decreased, the urine to be of higher specific gravity and thirst to be stopped, and at the same time the headache which so frequently accompanies this condition ceases."

Dysmenorrhea Pituitary therapy is indicated in cases of utero-ovarian hyperemia and in congestive dysmenorrhea (Dalché). This condition, however, is, in the great majority of cases, better treated by pluriglandular therapy (see "Dysmenorrhea," page 174).

Epilepsy B. R. Tucker[52] found that in some cases of epilepsy, which showed pituitary disease, pituitary therapy was of marked value. Sixty-three out of two hundred cases of epilepsy gave some evidence of pituitary disease. Such treatment is undoubtedly effective only in correcting a pituitary defect acting as a predisposing cause to epilepsy, and is not evidence of any specific effect in epilepsy in general.

Headaches Headaches of pituitary origin are fairly common. The location is characteristic, and seems to be between the temples, deep in behind the eyes. It is sometimes accompanied by

dyspituitary signs. Abnormality of the sella turcica is usually demonstrable. The headaches are usually amenable to treatment by the whole gland. This condition was first described by Pardee.[56]

Intestinal Paresis

Pituitary therapy may be successful in the treatment of intestinal paralysis and atonic conditions following abdominal and gynecological operations. Kirmissan[46] successfully used pituitary extract in paralysis of the intestines following operation for appendicitis. A subcutaneous injection of pituitary induced bowel passage after six days stasis. Chronic constipation is frequently relieved by continued oral administration of the whole gland, when the cause is loss of tone of the intestinal muscle coats (Bell). Graves[47] says: "Pituitrin has become a useful adjunct in the treatment of intestinal paresis and distention following abdominal operation. Some even go so far as to employ it as a routine. The first dose is given from four to six hours after operation and may be repeated a number of times at intervals of four to six hours, according to indication (Goetsch)." Osborne[48] also recommends solutions of post-pituitary in these conditions of postoperative intestinal paresis.

Labor—Induction of

Pituitary extract injected intramuscularly has been used for the induction of labor. Bell believes that pituitary not only increases the contractions of the contracting uterine fiber, but also sensitizes the non-contracting fibers, which then respond to mechanical stimuli and contract normally. Watson[57] reports its use for this purpose in 145 cases of his own and of his colleague. These were cases of dystocia, prolonged gestation, toxemia, pulmonary tuberculosis, etc. In 126 cases labor pains were induced. He injected ½ c. c. every half-hour. When the cervix dilated and the membranes began to bulge, the administration was discontinued. If the uterine contractions begin to weaken or occur at longer intervals, the dose may be continued. Bell uses pituitary injections in conjunction with the insertion of bougies.

A note of caution should be sounded in the use of pituitrin for this purpose. The advice of Mundell[58] is sound. He states that pituitary extract should be given only late in the second stage of labor, when the pains have become slow and weak, owing to uterine inertia, and in cases of normal presentation, dilated cervix and head moulded through the brim. Graves[59] also says:

> "It is in general contraindicated during the first stage of labor, the dangers being excessive pains on account of the powerful uterine contraction and rupture of the uterine wall, if there is weakness of the musculature or obstruction to the labor. Another danger is asphyxiation of the child in cases where subsequent rapid delivery cannot be carried out. * * * The extract is most useful during the second stage of labor in cases in which normal progress of labor has stopped. By its use low forceps operations are avoided, while in many cases, in which high forceps would ordinarily be necessary, delivery is brought about by a simple low forceps operation."

In secondary uterine inertia solution of post-pituitary is invaluable and usually produces a renewal of strong uterine contractions.

Menopause In the distressing and frequently acute symptoms attending the menopause, pituitary therapy is of value—symptomatically and as substitutive therapy. These symptoms are, however, pluriglandular. (See page 179.) Bell advises pituitary combined with calcium lactate as an agent for raising blood pressure to a slightly higher level, for the relief of the flushings due to variations of blood pressure, depending upon thyroid disturbance. The increase of blood pressure is no bar to the treatment of uterine sclerosis, which is frequent at the menopause and which is frequently the cause of metrorrhagia at that time. Dalché says that pituitary is valuable in this condition and in cases of flowing which occur as a result of the sclerotic condition.

Menorrhagia and Metrorrhagia Pituitary is one of the most potent agents in the treatment of menorrhagia. Pouliot states that, in chronic infection of the uterine appendages, amelioration of the uterine and periuterine engorgement is to be expected from the use of pituitary extract. The well-marked action of pituitary on uterine muscle is valuable in the treatment of intra-uterine clotting and lowered tone of the muscles. Bell regards pituitary as invaluable in the treatment of menorrhagia, caused by irregular action of the thyroid and ovaries, and in hypo-ovarism of puberty Dalché states that pituitary therapy is indicated. Here there is congestion and often menstrual and premenstrual dysmenorrhea, the pain arising with the appearance of the blood or three or four days before. Dalché supplements pituitary therapy with other treatment—hydropathy; cold water to the soles of the feet; warm applications to the upper surface of the feet, the anterior surface of the legs and the inner portion of the thighs; ice bag, etc. Treatment should be persisted in and attention devoted to alimentary hygiene, occupation, mode of life, etc. Block and Llewellyn [44] noted good results from the oral administration of pituitary substance in doses of from ½ to 1 grain t. i. d. in menorrhagia and metrorrhagia occurring at puberty. Osborne [45] says: "If there is no evident cause for menorrhagia, or for too frequent menstruation, in young girls, mammary extract represents the best treatment, although, if the girl shows signs of pituitary disturbance, a combination of these two glandular extracts will be of greater value." (See Menorrhagia, page 178.)

Metritis See "Sub-Involution."

Sepsis In puerperal infection and in all septic conditions, solution of post-pituitary is a useful therapeutic agent (Delille, Bell and others). In puerperal sepsis, whether limited or extending into the peritoneum, there is marked lowering of the blood pressure together with depression of all unstriped muscle, including that of the intestine. The intestinal paresis is a grave condition, predisposing to general intoxication through absorption from the intestinal canal. Pituitary therapy is, therefore, of value in both of the conspicuous and predominant symptoms of sepsis. The dose is larger than normal. Bell recommends 0.5 c. c. of the extract intramuscularly.

Shock Pituitary extract is a valuable agent in the treatment of and as a prophylactic for shock. Its use for this purpose is essentially the same as that of epinephrin. Any considerable loss of blood should be made up by replacing the fluid volume by transfusion of normal saline solution. If there has been no great loss of blood, pituitary extract alone may be used. The effect of pituitary is to raise the blood pressure and improve the regularity and force of the heart. One distinct advantage over epinephrin is the longer period over which the pressor effect is maintained. Bell has observed the increase of blood pressure to be maintained for a period of eight hours after a single injection.

Sub-Involution In acute cases, the action is direct and prompt; in chronic, some time must elapse for the effects, for here there is usually some detritus which must be gradually discharged by the pressor effect of pituitary. Bell advises the administration of calcium salts concurrently with the pituitary treatment.

Uterine Hemorrhage Pituitary extract is exceedingly effective in uterine hemorrhage and may be used alone and in conjunction with other measures. Its use is advised by Bell and by Pankow.[60] Pankow obtained good results and found that the periods became normal. Block and Llewellyn also found pituitary therapy efficacious in uterine bleeding. Graves,[61] in discussing post partum hemorrhage, says, "It (pituitrin) acts more rapidly than ergot, but its effects are more transient; hence the best effects may be procured by administering pituitrin first and following it later with ergot."

Contraindications

Pituitary preparations are powerful therapeutic agents and should be given only after careful examination of the patient. Particular care should be devoted to such examination before the use of intramuscular or intravenous injections. The general contraindications are:

Kidney disease.
Organic heart disease.
Cases of high blood pressure (posterior part).
Following operations on the intestines.
Arteriosclerosis.

In induction of labor it is contraindicated in disproportion between the fetal head and the mother's pelvis and in abnormal presentations.

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PART II

CHAPTER V

THE SEX GLANDS

GONADS

The sex glands are of interest in this work only as organs of internal secretion. In addition to their function in reproduction, the sex glands exert a striking influence upon the growth and development of the body, both physical and mental, and exercise important functions in metabolism and in the female in the process of menstruation.

THE TESTES

The testes in man descend in early life from the abdominal cavity, through the inguinal canal to the scrotum. The cells giving rise to the internal secretion are generally believed to be the interstitial cells or "Leydig" cells (puberty gland of Steinach). The cells of Sertoli, or sustentacular cells, are sometimes referred to as the place of origin, but this is not generally believed today.

> "If we summarize all that is known concerning the internal secretory tissue of the male genital gland, we are led to the inevitable conclusion that the hormone which gives to the organism its male characteristics is elaborated in the cells of Leydig in the interstitial tissue. In spite of their mesodermal origin, these cells are able actively to produce certain specific substances and to transfer these substances to the blood-stream; such being the case, we are justified in describing them in their totality as an 'interstitial gland.'
>
> "It is highly probable that, by the agency of its secretory products, this gland is responsible for the development of the male sexual gland from the indifferent genital trace. That it has a determining influence upon the normal development and maturity of the generative portion of the sexual gland, upon the formation of the secondary genital organs, and upon the existence and persistence of those morphological and biological characters which are the property of the male sex, is undoubted."[1]

The spermatogenic cells have been definitely eliminated from any function of this kind. In the human testicle the interstitial cells appear as collections of cells lying in masses which may fill up the spaces between the seminal tubules. They extend out to meet similar cells from other spaces, and then form a rather dense network throughout the body of the testis. There is no uniform arrangement, however, and they may appear as single cells only in the connective tissue stroma, from which they may be differentiated by their morphology and their stain reactions.

The interstitial cells arise from the columns of Pflüger and appear when the embryo has reached a length of about 25 mm. (about the 5th or 6th week). From that time on it exerts its remarkable effects in cell differentiation and the establishment of the secondary sex characteristics which form the striking differences between the sexes. (See pages 136 and 246.)

Wheelon[2] describes the developmental relations between germplasm and somatoplasm as follows, dividing the period of life from fertilization of the ovum to puberty into four periods:

"Primary Undifferentiated Stage. Potentially the fertilized egg carries sexual qualities. The presence of the germplasm, however, manifests itself only after marked development of the somatoplasm. In the primary undifferentiated stage of development sex cells are forming and may or may not be recognized histologically, hence sex can not be determined. Such a condition obtains in the developing human embryo until it has attained a length of 14 mm.

"Secondary Undifferentiated Stage. In human embryos 14 to 24 mm. in length sex cells may be definitely recognized. During this period organs are forming which later may develop into either male or female secondary sex organs, viz., the Wölffian and Müllerian ducts. Hence, the embryo is somatically sexually neutral, although germ cells of one sex are well established. Therefore, the developmental history of the sexual apparatus shows that the primordia of the genital organs are independent of that of the generative glands, and that the somatoplasm is primarily *indifferent* (bisexual) in character. * * *

"Primary Differentiated Stage. Immediately following the secondary undifferentiated stage vascularization of the sex glands occurs. Synchronous with the development of a blood supply to the germ cells there occurs a marked growth and differentiation of either the Müllerian or Wölffian ducts. The sexually indifferent character of the embryo is lost and secondary sex organs become established. This stage begins in the 24 mm. human embryo and continues throughout the adolescent period. Therefore, the differences that exist between tissues of male and female embryos do not make their appearance until the beginning of the period of primary differentiation or the time at which vascularization of the genital glands takes place.

"Secondary Differentiated Stage. At birth the secondary organs of sex are completely formed and continue to grow until the period of puberty. At this time, in the male, the germplasm becomes mature and active formation of spermatozoa begins. Modifications of bodily structure also occur which result in the establishment of the secondary sexual characters. Hair appears on the face, osseous changes occur, the voice becomes heavier and new nervous reactions develop. Sex and sex characters are completely established and sexual life begins. At puberty, as in the primary differentiated stage, the somatoplasm is modified according to the type of interstitial cell activity."

The interstitial cells apparently accomplish this differentiation either by the stimulation to development or formation of morphological characteristics in a previously neutral groundwork, or by the stimulation of one or the other types of cells in a hermaphroditic groundwork. Biedl [3] assumes that there is always present a hermaphroditic groundwork and the development of a male or female interstitial gland determines the sex characteristics by acting upon the characteristic embryonic cells of the particular sex:

> "It is only by the assumption of a hermaphroditic primitive genital trace, together with the dependence of the somatic and psychic sex characteristics upon the internal secretory activity of the genital glands, that we can explain those cases in which complete alteration of single sex characteristics, or even of the entire sexual character, takes place during the life of the individual."

With such an assumption, it is easy to understand how experimental suppression of the dominant sex tissue permits the development of the opposite type. The stimulation of one type of sex characteristics ordinarily prevents the development of the opposite type by mere overgrowth and predominance of the type receiving the stimulation of the interstitial cells. Robertson describes this as follows: [4]

> "We have in these facts evidence of specific hormones which stimulate the growth of certain tissues, those, namely, which give rise to the secondary sexual characters. This is not hard to understand, but if we regard this effect as arising from direct action of the hormones, the simultaneous inhibition of the opposite type of character is exceedingly difficult to interpret. We have seen, however, how the development of one type of tissue may suppress the development of another by prior appropriation of nutrients and the establishment of gradients of autocatalyst concentration, and we can understand in the light of these facts how a stimulator of one type of tissue growth may, by the very fact that the growth occurs, lead indirectly to the suppression of an alternative type of tissue growth. Let but the one type of tissue atrophy and the other, to the extent that atrophy has occurred, will tend to take its place. Thus, in human beings, and especially in the Australian aboriginal, the atrophy of the female generative organs at the climacteric is succeeded by a measure of development of male characteristics. Both possibilities are present. Which is to develop is determined by the inherited interstitial tissue. The development of the one type of tissue, and not the interstitial tissue itself, inhibits the development of the characters of the opposite sex."

If the groundwork is neutral, as assumed by some, no explanation is necessary for suppression of one or the other type. Biedl believes that castration before puberty results not in change to the opposite, but to an infantile or undifferentiated type. He believes castration removes the hetero-sexual elements, as well as the dominant sex tissue, and that we may find an example of true change of type in the case of women at the menopause who sometimes develop such male characteristics as deep,

masculine voice, hairy growth on face and body, etc. Here, he says, the ovarian inadequacy permits the hetero-sexual (male) rudiment to exert a determining influence upon the development of the primitive beginnings which are present in individuals of both sexes.

The experimental work supporting the theory of internal secretion control of the sex characteristics is very striking. In man, early castration prevents the development of the male voice and the beard. In Steinach's experiments on rats, castration prevented the development of secondary sex characters. These rats did not attempt cohabitation with the female. When testes were transplanted into these castrated rats, the immature seminal vesicles, penis, etc., developed, they energetically sought the female and carried out the sexual act. Histological examination showed the complete atrophy of the spermatogenic cells in these transplanted testes and the survival of the interstitial cells: convincing evidence of the function of the interstitial internal secretion in the development of the sexual organs and instincts. Steinach has also shown the effects of grafting gonads of one sex in the other, and has given further convincing evidence of the effect of the internal secretion in determining sex characteristics. Testes which are removed from their normal site are subject to change, the spermatogenic cells being chiefly affected. In cryptorchidism, the spermatogenic cells of the abdominal testis are usually atrophied.

Oslund [5] has shown that the germinal epithelium almost invariably degenerates when the testis is removed from its normal site and that any condition which raises the temperature is apt to produce this result. Such conditions are inclusion in the abdomen, high protein diet, alcohol, etc. Contrary to common opinion, he finds "that degeneration of the germinal epithelium results from displacement of the testis from the scrotum to the abdominal cavity, and that vasectomy alone does not cause degenerative changes in the testis."

From birth to puberty the interstitial cells do not increase much, but at that time they proliferate and increase rapidly, and this is the period of rapid and marked sexual differentiation.

Metabolism

The testes exert an effect in maintaining a normal rate of metabolism, as shown by the fall in metabolism following castration.[6, 7, 8]

> "The influence of the internal secretion of the generative glands is not confined to the development of the secondary somatic sex characteristics, but has a far-reaching effect upon a large number of organs and upon the general metabolism. The profound influence which this hormone has upon the organism is apparently independent of sex, and is thus not specific to the male or the female genital gland." [9]

This influence is in no sense comparable, however, to that of the thyroid or suprarenals. Increase in activity of the testis, such as occurs at puberty in man and in the breeding season in certain animals, is attended by increased metabolism. Injection of testicular extracts was described by Brown-Sequard as resulting in a feeling of increased vigor and general

well being, and similar results have since been recorded after careful experimental investigation. Zoth and Pregl[10] found that injections of testicular extract, given for a week in conjunction with systematic exercise, increased the muscular strength 50%, although the injections or exercise alone gave no results. Despite the lack of larger carefully controlled experimental observation, testicular extracts without doubt exert some effect in raising metabolism and creating a condition of strength and well being.

CLINICAL TYPES

Abnormalities of function of the internal secretion of the testes give rise to several distinct types. The extent of the deviation from normal will depend upon the age at which the disturbance arose and the length of time during which it is active.

HYPERFUNCTION	HYPOFUNCTION
Large sexual organs, with early functional activity.	Either the development of the tall, thin, delicate type, with long, slender arms and legs, narrow shoulders and broad pelvis, or the fat type, showing sluggish mentality and short, squat figure. In this there is a large deposit of fat in the abdomen, breast and hips. Loss of sexual desire and power.
Early development of mental and physical likeness to adult.	Small, undeveloped testes.
Early dentition.	Sterility.
Well-developed hair growth.	Absence of hair growth.
	Smooth, thin skin.
	High-pitched voice.

PREPARATIONS, DOSAGE AND ADMINISTRATION

Testis is used in medicine very largely as the desiccated substance (Orchic substance). Spermin was at one time heralded as the active principle of the testis, but the many claims made for it have not been verified or accepted. The "spermin" in all of a number of pluriglandular formulæ investigated proved to be plain orchic substance. Orchic substance may be given in a dosage of from 2 to 5 grs. three times daily. In hypogonad cases the dose may be larger.

THERAPEUTICS

Orchic substance is used in medicine very largely in the treatment of the sexual neuroses, impotence, as a general tonic and in the routine treatment of the aged, particularly for the reduction in size of the prostate. Orchic substance combined with prostate substance has been found of

value in this condition, and the combination of the two appears to be synergistic. Orchic-Prostate Comp. No. 5 may be used for this purpose. Gland transplantations, if they are successful, give all therapeutic effects, but as a surgical operation it does not meet the needs of general practice. Administered orally, the effects are good. Halsey [11] says:

> "After excluding many more or less unfounded conclusions, we may consider that the laboratory evidence is conclusive, that the testicle contains an internal secretion, which is contained in properly prepared extracts and which, when administered to a proper subject, can exert a specific effect on the sexual characteristics in certain animals and by inference probably in others."

Orchic substance may be successfully used in women and at times seems to act better than ovarian substance alone. (See page 176.) Lespinasse [12] combines adrenal and pituitary with testis:

> "The administration of fresh or dried testicle, adrenal gland and pituitary gland will stimulate both sexual libido and spermatogenesis."

Hormotone, which contains thyroid in addition to these glands, is thus indicated in impotence and the sexual neuroses.

Orchic substance is rich in phosphorus-bearing compounds, nucleo albumin, etc., and this has been held to account for its effects in medicine. Sajous holds their value to be dependent upon the adrenal principle contained in them. He is of the opinion that it has been shown by Poehl that spermin is a common element in both male and female and that this element owes its activity to "adreno oxidase," or the active substance of the adrenals (epinephrin).

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THE OVARIES

In like manner to the testes the ovaries also have an internal secretory function in addition to that of reproduction. In the case of the ovary, there is without much doubt more than one internal secretion: one produced by the interstitial cells and the other by the corpus luteum.

Interstitial Cells of the Ovary

The interstitial cells of the ovary occur as small groups scattered throughout the connective tissue stroma, and may be identified by both morphological and staining characteristics. This ovarian interstitial tissue gives every evidence of being an active secreting structure and has an abundant blood supply and cellular characteristics of glandular tissue. These and other facts to be described later have led to most writers classifying the ovarian interstitial cells as an internal secretory tissue, and performing for the female organism a function analogous to that performed by the testicular in the male. There is still, however, some difference of opinion on this point. Jaffe and Marine, in the Journal of Experimental Medicine, July, 1923, state, "These facts indicate that the interstitial cells of the testis and ovary are not functionally homologous." As first shown by Limon,[1] the interstitial cells of the ovary arise from the internal theca cells of the embryonic and prepubertal follicles. These follicles undergo some developmental changes and then degenerate. No ovulation ever occurs and both ovum and membrana granulosa degenerate and disappear, leaving the theca cells, which hypertrophy and form the peculiar masses of cells distributed throughout the ovary known as the interstitial cells. Biedl describes their origin as follows:[2]

> "The metamorphosis of the theca interna into interstitial tissue accompanies the degeneration of the membrana granulosa and of the ovum. When the ovum becomes destroyed, the cavity in the vesicle becomes filled with young connective tissue and shrivels; scarcely anything remains of the epithelium of the membrana granulosa, and the ovum is recognizable only as a small, shrivelled, hyaline lump in a mesh of the network of connective tissue. At this stage, the metamorphosed vesicle resembles a small corpus luteum, the structure of the cells of the theca interna having a resemblance to those of the corpus luteum. These metamorphosed vesicles may be termed spurious corpora lutea, or, better, atretic vesicles, and, in their totality, they represent the interstitial ovarian gland."

Secondary Sex Characters

In a great many species the interstitial cells do not appear to be found in the ovary. Whether they are actually present and escape detection or whether such functions are performed by other types of cells, still remains unknown. The generally accepted opinion at the present time, however, is that the

interstitial cells of the ovary through internal secretion effects determine the secondary sexual characteristics of the female. The evidence of the importance of the ovary in the embryo is less convincing than that relating to its effects at puberty. However, it seems to have been shown that in congenital absence of the ovary the uterus is either absent or undeveloped, and there seems no doubt that the internal secretion of the ovary definitely determines the development of the secondary sex characteristics. Steinach and others have shown that the ovary may even determine the secondary sex characteristics of the female when transplanted into the young castrated male. Lipschütz [3] has offered a more extensive argument in favor of this theory.

There seems to be but little doubt that, in addition to the internal secretion of the interstitial cells and the corpus luteum, the tissue of the follicle itself gives rise to an internal secretion exerting marked effects. Biedl states that it is responsible for the chemical corelationship of the ovary as a whole, and the maintenance of one important sex characteristic, the female genital tract, is dependent upon the follicles. In later life the influence of the ovarian internal secretion becomes unmistakable. Extirpation of the ovary results in failure of development or atrophy of the uterus. If the ovary is grafted into a young castrated guinea-pig, the mammary glands develop and the animal develops the characteristics of the female.

At the age of puberty the interstitial cells reach their highest stage of development and the most striking changes take place as a result of their activity. The mammæ enlarge and develop, the voice and contour of the body change, menstruation and ovulation are established, the uterus increases greatly in size and the immature girl, who has not greatly differed from a boy of similar age, becomes transformed into the woman. Along with these physical changes, there arises a marked difference in the psychic characteristics. All of these changes arise as a result of the internal secretion of the ovary. Ovariotomy at or after puberty is attended by very marked symptoms. If both ovaries are removed, there results a complete cessation of menstruation with a subsequent gradual atrophy of the uterus, obesity and atrophy of the external genitalia. The actual assumption of male characteristics by the female after ovariotomy has been reported. This would suggest the hermaphroditic groundwork assumed by Biedl (page 136). It is recognized that, in addition to these secondary sex differences due to the influence of the gonads, there may arise some characteristics due to the development of inherent growth tendencies in an asexual embryonic anlage as assumed by Tandler and Gross.

This latent tendency to development of the characteristics of the opposite sex is shown in the peculiar case of the sebright cocks. In the sebrights the male is normally hen feathered. If they are castrated, they develop the long feathers and colored plumage of the ordinary typical cock. In the female ovariotomy also results in the development of the plumage of the cock. In the case of the cock the interstitial cells must be similar to those in the ovary, at least in its effects on feathering, for it stimulates the growth of the female type of feathering. The latent tendency to the male type of feathering is, however, present in both sexes, as evidenced by the male type of plumage, which develops when the influence of the female type of interstitial cell is removed.

At puberty, or the beginning of the period of sexual activity, three striking events are initiated, ovulation, menstruation and the development of a new, unusual type of endocrine structure, the corpora lutea. All of these are intimately related to each other, and but brief mention of these interrelated processes can be made here (see page 167).

Menstruation and the Corpus Luteum

Menstruation represents the failure of conception and a step in the preparation for the new ovum. The full maturation of the follicles probably determines the premenstrual endometrical changes. Following the rupture of the follicle and the discharge of the ovum the corpus luteum develops in the ruptured follicle, which at first collapses. The theca cells and those of the granulosa grow together and finally from one or the other arise the characteristic yellow lutein cells. Into this mass from the theca cells extend fibroblasts and later also capillaries extend to vascularize the mass, so that a definite organized structure—the corpus luteum—finally occupies the old follicular space. The corpus luteum is definitely a structure with an internal secretion and inhibits the development of the follicles and sensitizes the endometrium for the reception of the ovum. The endometrical changes and the development of the corpus luteum (which begins development just following ovulation) proceed together and, if pregnancy does not occur, menstruation with its destructive effects on the endometrical mucosa takes place, the corpus luteum begins to degenerate and a new ovulation starts the process all over. If pregnancy occurs, menstruation fails to take place, and the corpus luteum persists (the corpus luteum vera).

The corpus luteum, therefore, inhibits ovulation and sensitizes the endometrium. It does not initiate menstruation, which is a degenerative process of the endometrium resulting from the failure of conception. A complete menstrual cycle is probably as follows:

1. Ovulation and the subsequent development of the corpus luteum. For approximately 15 days the corpus luteum exerts its effects in sensitizing the uterine mucosa and repressing further ovulation.

2. Menstruation takes place, a degenerative process of the endometrical mucosa as a result of failure of conception. Concurrently, the corpus luteum degenerates. This period lasts for from one to three days. The menstrual flow and degeneration of the corpus luteum take place concurrently. This does not mean that the corpus luteum is the direct cause of the menstruation.

3. The new ovum now begins to develop (in the absence of any restraining influence of the corpus luteum), follicular and ovum growth proceeds with the attendant or consequent hyperplasia of the uterine mucosa. This period lasts for ten days and is followed by No. 1 above. This completes the cycle.

There is also strong evidence that the corpus luteum exercises an influence on the growth of the mammary glands. Mammary growth is inhibited by removal of the ovaries and corpus luteum and failure of development of corpus luteum is observed to be accompanied by failure of growth of the breasts.

Effects on Metabolism

Löwy and Richter[4] calculated the metabolism in castrated dogs and found it to be reduced from 14 to 20% per kilogram of body weight, a reduction which might be maintained for years. This has also been shown by Luethje, Murlin and others. Of the gonad effect on metabolism Beidl says:[3]

> "This theory is very strongly supported, however, by the discovery that it is possible to raise the depressed metabolism to as much as 30 to 50% above the normal by the exhibition, either subcutaneously or by the mouth, of ovarian or testicular substance. In normal, sexually mature animals, the exhibition of these substances is entirely negative. In the case of castrated animals, both male and female, the ovarian substance was found to be the more active, the effects of testicular substance being slight in males and negative in females."

Biedl believes that the increased metabolism resulting from administration of ovarian and orchic substance is due to the consumption of non-protein matter, as it has been shown that protein metabolism is not affected by the gonads.

CLINICAL TYPES

Hyperfunction	Hypofunction
Rapid early growth.	Obesity.
Early dentition.	Lowered basal metabolism.
Early menstruation.	Immature mammary, gonads and secondary sexual development.
Early appearance of pubic and axillary hair.	Tall skeleton.
Precocious development of mentality and sexual organs.	Amenorrhea or irregular menstruation.

PREPARATIONS, DOSAGE AND ADMINISTRATION

Ovarian preparations used in medicine are desiccated whole ovary, corpus luteum, ovarian residue (ovary without corpus luteum), and ampoules of corpus luteum and of whole ovary. Desiccated ovary, ovarian residue or corpus luteum may be given in a dosage of from 2 to 5 grains three times daily. Ampoules may be given two or three times weekly, or oftener in the case of urgent conditions, such as the vomiting of pregnancy. As to the therapeutic differences between the various ovarian preparations, Graves says:

Therapeutic Differences of the Several Ovarian Preparations

> "Thus it happens that there is a very wide divergence of opinion among clinicians in the matter of ovarian therapy. Many assert that the administration of ovarian substance is entirely valueless in any condition. Such testimony may, however, in the light of recent experience be disregarded. The chief controversy lies in the question as to which part of the ovary is most efficacious therapeutically, some advocating the corpus luteum alone, others the entire ovary, while, as will be

seen, the author recommends the ovarian substance from which the corpus luteum has been excluded. Experience shows that all these three preparations have essentially similar physiologic effects when used in certain conditions, variations occurring only in the intensiveness of the results. It may be said that in all preparations the most striking results are obtained in the treatment of the vasomotor symptoms of the menopause. All of them will benefit a certain number of cases of amenorrhea and oligomenorrhea and of circulatory disturbances of the external genitals. It seems probable, therefore, that the active substance is the same, whether the extract be made from the corpus luteum or from the rest of the ovary. Therefore, in selecting a part of the ovary for the extraction of the secretory substance, it is a matter of choosing that tissue which shall yield the substance in greatest abundance, and with the least toxic effect on the patient.

"Present knowledge indicates that there exist both in the corpus luteum and in the atretic follicles cellular elements identical in their origin from a specific connective-tissue structure (the theca interna) and capable of producing an internal secretion which is important to the growth and normal functioning of the organism. If this is true, we have a basis on which to found a rationale for ovarian therapy.

"If an internal secretion is manufactured from both the corpus luteum and the atretic follicles by cells of identical structure, extracts made from the corpus luteum alone lack that valuable part of the secretion which is derived from the atretic follicles. Moreover, it is impossible to tell by inspection whether a given corpus luteum is in the process of maturation or at the height of its development, or in a stage of involution and disintegration. It must happen that in the preparation of many corpora lutea for therapeutic purposes a varying number are included in which the essential cells are no longer active as organs of internal secretion, and are actually in a condition of dissolution. We should expect, therefore, that commercial preparations of corpus luteum would present a wide variation in their therapeutic effects, and, owing to their readiness to decompose, would have a special tendency to become toxic.

"On the other hand, if the preparation be made from the whole ovary, including corpus luteum, stroma and follicles, the important follicular secretion is not lost. Preparations of this kind would be expected to be more stable in their composition and more constant in their effect than those of the corpus luteum alone. These conclusions have been amply borne out by our clinical experience." [5]

Ovarian Lipoids

The active physiological principle or principles of the ovary are as yet unknown chemically. This applies to the whole ovary, the corpus luteum, or the ovary without corpus luteum. The active principles, however, are generally recognized as being lipoids or contained in lipoids. The necessity for retaining the lipoid

substances in ovarian preparations and the danger of degreasing is recognized. Yet, despite the proof from both experimental physiology and clinical medicine, the product of the greater number of manufacturers is degreased and its potency reduced in direct proportion to the thoroughness with which this is carried out. The following statement from two of the best known workers in the field may be quoted:

> "Although I have not written to all the manufacturers in the United States, I understand that practically all of them resort to degreasing processes. This makes a finer and smoother product from a commercial viewpoint, but there can be little doubt that it diminishes the therapeutic effectiveness of the preparation."[6]
>
> "This leads me to state that to-day we have no better ovarian extract on the market than we had in 1910, when I first discussed this subject. The commercial preparations are 'degreased' or 'defatted' and, therefore, deprived of such minute doses of the active principle as they may have originally contained. Pharmacologically, they are inert. This includes the ovarian extracts, corpus luteum extracts, ovarian residue, ovarian substance, etc."[7]

The sole reason for defatting seems to be, as suggested by Novak, the production of a finer pharmaceutical product, but surely no considerations of "fine pharmaceutical product" justify the marketing of a worthless preparation for the treatment of disease. Moreover, experience with the product of a manufacturer* which is not degreased has clearly shown that it is stable, shows no objectionable characteristics and retains all the potency of the lipoids of the ovary and corpus luteum.

Success in the preparation of such a product, leaving the lipoids intact and not subject to decomposition or bacterial change, depends primarily upon an efficient method of desiccation. Professor Rogers says:[8]

> "The defatting process is necessary for the removal of the lipoids which prevent drying and so produce putrefaction. There is, however, a method apparently not yet in commercial use, by which animal tissues can be dried without change except in the removal of water."

The Carnrick product probably owes its high therapeutic efficiency to the high degree of desiccation, accomplished without high temperature and permitting the retention of the lipoids in a stable product. Degreasing from the pharmaceutical point of view is, therefore, unnecessary.

The term lipoid was introduced by Overton in 1899, to describe substances which resemble fats in their solubilities. It has no definite chemical meaning and includes such substances as phospholipines (lecithin), lipines, cholesterol, etc. The interest in the lipoids has always been more biological than chemical, and has related to the solubilities of substances in lipoids and of lipoids in various solvents (as living cell membranes are lipoid in character). The original conception of lipoids as substances which are soluble in fat solvents is that held today and the use of selective solvents in separating these substances is not far developed. Although some simple

* G. W. Carnrick Co.

examples are known, such as the removal of fat without lecithin by acetone, it is out of the question to attempt to work with selective solvents when the nature of the lipoid we desire to retain is unknown.

The lipoids of the ovary are the active internal secretion elements. Iscovesco was the first to demonstrate this fundamental fact.[9] He isolated two principles, II Fb. and V Dc. which are soluble in alcohol and ether. Herrmann,[10] Seitz, Wintz and Fingerhut,[11] Aschner,[12] Frank,[13] and Frank and Rosenbloom[14] have also isolated the lipoids of the ovary, which undoubtedly represent the active physiological principle.

Rogers[8] found the lipoids the active substances, the removal of which destroys the therapeutic activity of the product:

> "In some preliminary experiments conducted at Cornell by Dr. Blau, from the Department of Chemistry, in conjunction with Dr. Papanicolaou, in the Department of Anatomy, to determine the comparative effects of different derivatives of the ovary upon the guinea-pig's œstrus cycle, there have been obtained some very suggestive results. All of the defatted or common commercial desiccated ovarian materials are either uncertain in their effects or inert. Of the extracts of fresh glands, those made with alcohol or glycerine seem the most active, and both of these kinds of extracts contain more or less of the lipoids."

In view of the fact that the chemical nature of the active principles of the ovary is unknown, but that it is of the nature of a lipoid, it would seem that the removal of fat with solvents, which also remove the lipoids, or by any process (for the lipoids are fat soluble), would be unjustifiable. The following advice of a group of research workers in this field is of the very soundest sort:[15]

> "In seeking to demonstrate the presence of therapeutic principles of unknown chemical nature as we are called upon to do in ovarian therapy, we must seek to prepare the gland for therapy in a fashion to give the greatest likelihood of conserving those principles. Such preparation ideally demands the use of a technic calculated to preserve every chemical entity in the gland."

With a proper, potent preparation, ovarian therapy is not only successful, but is effective in a class of cases for which there is no other known direct medicinal therapy.

THERAPEUTICS

The field of ovarian organotherapy is described by Graves as follows:[6]

> "The therapeutic value of extracts of ovarian substance has passed beyond the stage of theory and speculation and is now an established fact beyond all doubt. With regard to the nature of the active substance, the exact location in the ovary of its manufacture, and many other questions we are still considerably in the dark. The earlier reports of the use of ovarian extracts were, for the most part, discouraging, but in recent years better preparations, a more definite knowledge of the physiology of the ovary,

and a more intelligent selection of cases for treatment have yielded results that are not only satisfactory, but often astonishing.

"The value of ovarian therapy is seen in the treatment of patients who are suffering from functional deficiency or absence of the ovarian internal secretion. The most conspicuous examples of this are those who experience the vasomotor disturbances of the natural or artificial menopause, the symptoms of which consist chiefly of hot flushes, vertigo, etc. By the administration of a properly prepared extract these symptoms are, with some exceptions, greatly benefited or made to disappear entirely. The extract is, therefore, of the greatest help in the routine postoperative treatment of patients who have undergone hysterectomy, at least 80% of whom suffer from vasomotor changes.

"Next to its importance in menopause cases is its value in treating young women with functional amenorrhea and oligomenorrhea. Its results with these patients are not as constant as in the first class of cases, but its use is here successful, either partially or completely, in the majority of instances.

"A third type of cases in which ovarian therapy is surprisingly efficacious is represented by patients suffering from deficient circulation of the external genitalia. As is elsewhere stated, animal experimentation has proved that the ovarian internal secretion has a specific hyperemic effect on the external genitalia. Substantiation of these experiments on animals is seen in the beneficial effect which ovarian extracts have on conditions of pruritus, kraurosis, furunculosis, and other affections of the vulva in elderly women where the local disturbance of the parts is due to inadequate circulation. * * *

"In the treatment of the foregoing classes of cases the evidence of the value of ovarian organotherapy is beyond dispute, and is entirely substantiated by a large experience in its use by the author.

"In addition to these three types, various other gynecologic affections are reported to be greatly benefited by ovarian extract. Burnam has had marked success in treating neurasthenic underpar women in the preclimacteric decade. Dannreuther reports success in bringing a patient to term after repeated abortions, and finds the treatment helpful in the hyperemesis of pregnancy."

In a recent article in Endocrinology,[8] Novak makes a critical review of the present-day application of ovarian therapy. The history of this form of organotherapy is briefly reviewed from the beginnings in the Landau clinic in 1896 and the use of corpus luteum by Burnam in 1904 to its present widespread usage.

Despite the skeptical tone admitted by the author, deliberately chosen for the reason that he believes that in the field of endocrine therapy it is safer to err on the side of hyper- rather than hypo-skepticism, there is an undeniable note of confidence in ovarian therapy.

"In spite of the confession of unsatisfactory results embodied in this paper, I am frank to say that I employ ovarian therapy for

certain indications, because I believe it to be based on rational principles, and because it is reasonable to hope that the biological chemist will sooner or later succeed in giving us ovarian extracts which will really approximate in their effects the action of the ovarian secretion *intra vitam.*"

A careful reading of this article leads to the conclusions that:

1. Ovarian therapy has a real field in medicine, but, as in other forms of organotherapy, it should be used with discrimination and should not follow the ill considered, if enthusiastic, claims in much of the literature.

2. Pluriglandular combinations are more effective in many conditions than single gland extracts.

3. The future of ovarian therapy in medicine is assured and will eventually reach the precision of thyroid therapy.

As to the rationale of ovarian therapy, Novak states: "The known facts as to the physiological effects of the ovary are sufficient to supply a logical basis for the general idea of ovarian therapy." A brief consideration of the known physiologic effects of the ovary and the corpus luteum, obtained largely through a study of the effects of ovariectomy, suggests the value in treatment.

Among the therapeutic uses of ovarian preparations considered by Novak are amenorrhea, menopausal vasomotor symptoms, dysmenorrhea and genital hypoplasia, vomiting of pregnancy, sterility and obesity. Its uses in amenorrhea, menopausal conditions and obesity are quite definite. The use of corpus luteum in the vomiting of pregnancy was originally introduced by Hirst, of Philadelphia. For this purpose, it may be given as Corpus Luteum Comp. No. 6. Hypodermatic administration is frequently necessary and corpus luteum ampoules are prepared for this purpose (see page 250). Ampoules by injection, as a supplement to the oral administration of the Corpus Luteum Comp., may be effective. As has been suggested in Graves' valuation (above) of the several ovarian preparations, precise therapeutic differentiations of the fields of usefulness are not possible in the present state of our knowledge. However, from theoretical considerations, that proposed by J. C. Hirst, in the *New York Medical Journal* of October 5, 1921, seems as useful as any proposed:

Whole ovary in:

1. Natural menopause.
2. Surgical menopause.
3. Late establishment of menstruation.

Ovarian residue in:

1. Late development of puberty.
2. Infantilism.
3. Irregular menstruation at puberty.
4. Menorrhagia of youth.
5. Obesity and amenorrhea.

Corpus Luteum in:

1. The control of the nausea of pregnancy.
2. Habitual abortion without demonstrable cause.
3. Menopause (less efficient than whole ovarian extract).

4. Scanty menses or functional amenorrhea of youth.
5. Pruritus vulvæ in elderly women.
6. Sterility.

The uses in gynecological conditions are treated in the following pages:

Amenorrhea, page 172.
Dysmenorrhea, page 174.
Menopause, page 182.
Menorrhagia, page 178.
Sterility, page 184.
Vomiting of pregnancy, page 148.

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PART II

CHAPTER VI

THE THYMUS GLAND

ANATOMY

The thymus gland is an organ of two lobes, subdivided into lobules, composed of a cortex and medulla, the cortex made up of lymphocytes packed together in a dense, solid arrangement, and the medulla made up of a cell network, in the meshes of which are large numbers of lymphoid cells, in the characteristic concentric figures—the corpuscles of Hassall. The cortex is very vascular and resembles the structure of a lymph gland. The cells are strongly lymphocyte in character and are densely packed together. These cells are either actually modified lymphocytes which have migrated into the tissue or they are of epithelial origin. Some small granular cells of the thymus have an amœboid movement and are believed to possess the ability to transform into plasma cells. The medulla is not so densely packed with cells as the cortex and is made up of larger epitheloid cells, showing much branching. It does not contain as many leucocytes as the cortex. The distinguishing characteristic of the medulla are concentric bodies, the corpuscles of Hassall. These corpuscles frequently become infiltrated with lime salts or show fatty changes. Their function is unknown.

The gland lies in the mediastinum, in close relation with the large blood vessels and the pneumogastric, recurrent laryngeal and phrenic nerves. It is covered with a well-defined, tough capsule.

EMBRYOLOGY

The thymus is developed from the epithelium of the third branchial pouch on each side. Occasionally it may arise from the fourth. These pouches subsequently grow together and form a solid structure which undergoes lobule formation and branching. The branches or buds develop as solid epithelial outgrowths from the lower end of the main solid structure on each side, giving rise to a lobulated appearance. These buds grow together and form a single structure by uniting in front of the trachea.

BLOOD SUPPLY

The blood supply is from the internal mammary artery, and occasionally from the inferior thyroid in addition. The veins leave the thymus to empty into the left innominate, and frequently into the internal mammary and inferior thyroid.

NERVES

The nerve supply is not elaborate. Small branches form the cervical sympathetic. The pneumogastric or the phrenic may sometimes be found.

of Park and McClure,[4] analyzing the results of thymectomy appearing in the literature. The early work of Klose and Vogt apparently showed that the thymus was essential to life and very largely influenced growth and development, and particularly calcium metabolism. M. H. Hoskins,[5] reporting the results of thymectomy and thymus transplantation in tadpoles, states that "none of the operations performed seems to have affected the growth and development of the animals." The results corroborated the opinion of Allen, that the thymus is not necessary for the life and development of the tadpole and that extirpation has no effect on the thyroid and gonads or spleen. Downs and Eddy[6] also found that injections of large doses of desiccated thymus substance in young rabbits did not impair growth or development. They reported, however, a considerable increase in weight in the thyroid and spleen, and a decrease in the weight of the thymus.

Basch[7] apparently showed some function of the thymus in calcium metabolism as a result of extirpation experiments, principally on dogs, which developed a condition resembling rickets and which showed a marked reactivity to the galvanic current upon stimulation of the peripheral nerves. Klose and Vogt outlined a series of changes following thymectomy, which are summarized by Vincent as follows:[8]

> "(1) A latent period, lasting from two to four weeks;
> "(2) An adipose stage, which lasts two or three months; and
> "(3) A cachectic stage, or the stage of 'cachexia thymopriva.'
> This period extends from three to fourteen months. Death occurs with 'coma thymicum,' which often lasts a long time. The skeleton remains hypoplastic and dwarf-like, and the bones become atrophic. There is a deficiency of undissolved calcium. Bodily movements are feeble, and there are disturbances in the nervous system."

These observers formulated a theory that the thymus functions in fixing phosphoric or nucleic acid, and that thymectomy permits the accumulation of these acids with removal of calcium and resultant defects of bone growth and symptoms of the nervous system.

The experiments of other workers have also resulted in abnormalities of bone growth, production of muscular weakness, etc. Howell believes that the thymus plays a part in preventing or neutralizing excessive accumulation of acid in the body, others have suggested that it plays a part in the immunity reactions.

A survey of the literature will show that there is remarkably little upon which to base an opinion that the thymus is a gland of internal secretion. The observations as to its interrelationship with the generative glands and its effects on bone growth and development, however, are strongly suggestive. Uhlenhuth[9] asserts that his experiments have demonstrated the production of an internal secretion with a toxic effect, causing a condition of "tetania parathyreopriva." In many observations, the spleen seems to undergo compensatory hypertrophy in cases of thymus ablation and in a large percentage of cases of Graves' disease the thymus is hypertrophied. Its relation to the sex glands has been referred to.

MORS THYMICA

The very unusual and peculiar condition, the chief characteristic of which is sudden death in infants and children apparently in good health, is termed Mors Thymica. Post mortem examination usually reveals a hyperplastic enlarged thymus, although frequently not large enough to make it appear likely as a cause of death. Two explanations are held as to the cause, one the pressure theory and the other the theory of systemic disturbance (intoxication). The literature records a sufficient number of cases to make certain that "Mors Thymica" is a clinical entity, although the symptoms show much inconstancy. Hammar, however,[10] states that there is no evidence that "Mors Thymica" is due to an abnormal condition of the thymus, and that the condition must be clearly differentiated from "Thymic Asthma," in which "it seems to be proved quite conclusively that in certain cases of this kind it really is the thymus that has produced the fatal symptoms by pressure on the air passages." This condition will now be described.

THYMIC ASTHMA

If the thymus is sufficiently large to produce pressure symptoms, the condition of thymic asthma may develop. This appears to be almost wholly a condition arising in infancy. As in "Mors Thymica," there is much uncertainty concerning this condition, and it has been denied that such a syndrome exists. Surgery and x-ray treatment may be necessary.

STATUS THYMICO LYMPHATICUS

This condition is generally regarded as a constitutional disease associated with abnormal development of the thymus and the lymphatic system. Falta describes status lymphaticus, which he differentiates from status hypoplasticus as follows:[11]

> "In true status lymphaticus the involution of an already abnormally developed lymphatic apparatus remains absent. We find enlarged follicles at the base of the tongue, hyperplasia of the entire pharyngeal lymphatic ring, lymphoid growth in the nose, enlargement of the lymphatic glands in the neck, in the axillary and inguinal regions, hyperplasia of Peyer's patches, red bone marrow, large spleen, and more or less large thymus gland. Very frequently we found hypoplasia and narrowness of the aorta and the whole arterial vascular tract. The heart likewise is often abnormally small, although it can also be hypertrophic. Commonly there is dilation of the left ventricle with diffuse clouding of the endocardium, and not rarely remaining behind in the development of the genitals, slight development of the secondary sexual characters, retarded onset of menstruation, and retarded, lessened, sexual instinct."

The condition is much commoner in males than in females. The etiology is unknown. Some relation to chromaffin deficiency has been suggested.

CLINICAL TYPES

States of hypofunction can not be outlined clinically. The characteristic signs and symptoms of Status Thymico Lymphaticus are as follows: Enlarged thymus and symptoms of difficult breathing and asphyxia: abnormalities of skeletal growth; symptoms due to congenital underdevelopment of the cardio vascular system—irregular and weak heart action, etc.; asthenia; thin white skin; enlargement and hyperplasia of the lymph nodes and lymphatic system; lymphocytosis; middle incisors larger than the lateral; undeveloped genital organs; hair distribution and physical contour of the hetero sexual type; weak muscles and tendency to fatigue.

PREPARATIONS AND DOSAGE

Thymus is used in medicine as desiccated thymus substance of the calf. It is prescribed either in capsules or in tablets, in a dosage of 3 grains, and is administered by mouth.

THERAPEUTICS

Thymus has been used in infantile marasmus and atrophy, exophthalmic goitre, hemophilia, chlorosis, rickets, chorea, arthritis and a variety of conditions for which there is remarkably little positive evidence of value. Its use in exophthalmic goitre, while probably not of great value, would appear from the literature to be worthy of trial in some cases. Its use in deficient development and defective bone formation in infants may have some value. Sajous states that in rickets it is of undoubted value in some cases. Its use in arthritis deformans, rheumatoid arthritis, etc., would appear to be amply justified, particularly as our effective therapeutic agents for these conditions are very limited. Such a use is entirely empirical, but the clinical experience has shown that it is possessed of some value for this purpose. Thymus Comp. may be used for this purpose, and contains a small dosage of thyroid.

CONTRAINDICATIONS

In any cases of leucocytosis, thymus therapy should be used with caution.

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PART II

CHAPTER VII

PINEAL GLAND

EPIPHYSIS CEREBRI—CONARIUM

The pineal gland is a vascular body, oval, smaller than the pituitary and projecting from the roof of the third ventricle. It is joined to the cerebrum by two crura, the peduncles of the pineal gland. It lies in front of and between the corpora quadrigemina. The pineal is larger in children than in adults, and in females than in males.

The pineal body has a lobulated structure, the cells irregularly arranged in trabeculæ, between which are the large blood vessels. The interlobular tissue is composed of connective tissue and, in some animals, of muscular tissue. The peculiar substance "brain sand," made up of calcium phosphate and carbonate, is found in the interlobular tissue and the covering of the pia mater and, in some cases, in the peduncles. The average weight of the epiphysis is about .21 gram. It develops from the epiphyseal pouch in the third ventricle, from which in some reptiles a median eye is developed. Professor Tilney (Address at March 5, 1918, Meeting of the New York Neurological Society), however, believes that the morphologic evidence definitely refutes the claim that the pineal is a vestigial organ, or the vestige of an eye in lower forms. The pineal undergoes degenerative changes in adult life and its metabolic and functional activities are conspicuous before puberty. There has been a wide divergence of opinion among authors as to whether the pineal is a structure with a true internal secretion, and, while this uncertainty still finds expression in the literature, there seems to be a predominance of opinion that it is an internal secretory organ. This opinion is expressed by Tilney,[1] who states that he "had been forced to the conclusion on the strength of my findings, that it was without question in mammals and man an important endocrine gland, contributing the products of its secretion to the blood stream and functioning in the interests of bodily metabolism."

PHYSIOLOGY

The functions of the pineal are not well understood. Clinical observations and animal experiments strongly indicate that it is concerned in the growth and development of the sex organs and of somatic growth in general. The experiments carried on have been almost entirely by means of feeding or injection experiments and of pineal extirpation. The results of these methods are curiously in conflict. It has been noted that injection and feeding of pineal substance produce a more rapid growth than normal and bring about early sexual maturity, and feeding experiments in general lend support to the theory that the pineal accelerates

development. McCord found that pineal feeding increased growth remarkably. In Dana and Berkeley's experiments, they found that in a series of twelve guinea pigs six pineal-fed pigs increased their weight 325%, whereas the controls increased but 250%, and in rabbits, experimental animals averaged a gain of 1442.5 grams per rabbit, while the controls gained but 1074 grams per rabbit. McCord [2] found in his experiments that the experimental animals gained an excess of 23% over the control group, and he concluded that the administration of minute quantities of pineal to young animals stimulates rapid growth of the body. Extirpation experiments show, in some cases, a more rapid bodily growth and a more early development of the testes and sex characteristics. Some observers, such as Sarteschi,[3] have reported that in some of their experiments the macrogenitosomatic syndrome was produced in young rabbits and puppies. Others, Foà [4] and Izawa,[5] using the cock as the experimental animal, reported excessive growth of the sexual organs, comb and secondary sex characteristics following pinealectomy. Others, such as Exner and Boese,[6] and Biedl,[7] find no changes resulting. Horrax,[8] who has made some of the most extensive experiments on this subject, found that gonadal growth is appreciably stimulated by the removal of the pineal. Dandy,[9] in very carefully observed experiments, found nothing to support the view that the pineal gland inhibits the sexual function, or that its removal is followed by excessive sexual development. The contradictory results of extirpation and feeding and injection experiments have not been reconciled. McCord [10] offers two possibilities in explanation. First: Precocious macrogenitosomatic syndrome may result from disturbing the general endocrinous balance, either by increasing or decreasing the amount of the pineal secretion available for the body's use. Second: The cells of neoplasms involving the pineal gland may retain some of the metabolic and other functional characteristics of the normal pineal cell from which they were derived, and the peculiar bodily, sexual and mental changes in patients with such tumors may be manifestations of increased rather than decreased pineal activity.

The theory that the pineal exerts an inhibiting effect on the development of the sexual organs before puberty is usually referred to as the Marburg-Pellizzi hypothesis,[11] which has been established principally on the basis of pathologic findings, in which tumor formation of the pineal was believed to result in hypopinealism, with a consequent hypertrophy of the gonads. However, there is no agreement that the tumor formation which occurs in this class of cases lessens the function. Many observers maintain that the functional capacity is increased.

Smith Ely Jelliffe,[12] in his discussion of this theory, states that in the final conclusion of the matter it may be assumed that Pellizzi's syndrome of macrogenitosomia may be related to increased rather than diminished activity of the pineal gland.

CLINICAL TYPES

The characteristic syndrome of pineal involvement, independent of local symptoms due to pressure, etc., is described by McCord as due to

disturbances of metabolism. They are noted in children before the age of puberty. They are:

Signs of early sexual maturity:
- Enlarged sex organs;
- Pubic hair;
- Precocious development of body hair;
- Early change in voice.

Precocious mental development:
- Maturity of thought and speech;
- General bodily overgrowth.

PREPARATIONS, DOSAGE AND ADMINISTRATION

Pineal preparations are administered as desiccated gland substance, manufactured from the pineal glands of young bullocks. Preparations manufactured from the glands of adult animals have been found to lack in activity. Pineal may be administered alone in tablets or in powder form, or it may be combined with other gland substances. It is administered almost without exception by mouth. The dosage is from 1/20 to 1/10 of a grain.

THERAPEUTICS

The results of animal experimentation encouraged the use of pineal substance in clinical medicine, and the first reported experiments are those of Goddard and Cornell. Since that time it has had a fair use in medicine. Osborne [13] states that, while pineal gland treatment in children who are defective is experimental, "however, in children who are delinquent and do not show distinct indications of other glandular insufficiency, small doses of pineal extract may be given. Tablets of pineal extract may be obtained for such administration which represent 1/20 of a grain. Theoretically, such a dose need not be given more than once or twice a day." In children up to 12 to 15 years of age, with low mentality and evidence of retarded bodily development, Pineal Comp. Nos. 3 and 4 may be prescribed.

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PART II

CHAPTER VIII

PLACENTA

The function of the placenta has been the subject of speculation from very early times. The physiologist, Johannes Müller, is usually stated to have been the first to suggest an internal secretory function, a theory which subsequent investigation has served to support, so that today it is generally considered that, in addition to its other functions, the placenta gives rise to definite internal secretion effects. Halban [1] considered that the placenta was responsible for mammary development during pregnancy and exercises an effect similar to that of the ovaries, which are not active during this period. This theory is supported by the experiments of Herrmann, who isolated a lipoid from the corpus luteum which was biologically and chemically identical with a lipoid extracted from the placenta. These lipoids exerted an effect of growth stimulation on the mammary glands.

Halban believed that the placenta was responsible for mammary development and the initial stage of colostrum formation, but that the placenta prevented the subsequent actual formation of milk. Frankl [2] corroborated this view by transplanting the placentas of mice under the skin of another pregnant mouse. The placentas of pregnant mice within 10 or 12 days of term were transplanted into mice of approximately the same stage of pregnancy. He says:

> "In this third group of successful transplants the following results were observed: Mice, from a strain known to be able to nurse satisfactorily their young, would have litters of five or six. The newborns would seem normal in their appearance and would immediately begin to suck the mother animal. But they invariably died within the next five to seven days, evidently from starvation. Investigations showed that the mamma of the mother animal was secreting colostrum and not milk. In the unsuccessful transplants of the first and second groups lactation proceeded normally. A successful transplantation of a placenta on a pregnant animal causes persistence of colostrum secretion."

Apparently the placenta substitutes for or supplements the action of the corpus luteum in its effects on mammary development during pregnancy. Such an action of the ovary in stimulating mammary development had previously been shown by O'Donoghue, Bouin, Ancel, Knauer and others.

LACTATION

The researches of Starling and Lane-Claypon resulted in the formulation of an interesting theory relative to the fetal mass itself in lactation. Using the virgin rabbit as an experimental animal, they produced by

the injecton of fetal extract a development of the mammary glands resembling that occurring during pregnancy. Under like conditions, extracts of other organs—ovary, placenta, etc.—failed to produce any such change. Observing that after delivery the mammæ actively secrete milk, they conclude that an internal secretion found in the fetus stimulates the development of the breast and, at the same time, inhibits the actual mammary cell degenerative changes constituting lactation. After the inhibiting influence of the fetus is removed at birth, lactation begins. In connection with the development of the mammary glands, the influence of the internal secretion of the corpus luteum should be noted. This has been shown by O'Donoghue and by Ancel and Bouin. Puncture of the Graafian follicle and production of an artificial corpus luteum is attended by growth of the mammæ.

Foà and Basch also demonstrated the effectiveness of fetal extracts in stimulating mammary growth; so that it is likely that it is not the placenta alone which is active in producing the growth effects. In establishing lactation, the influence of the nervous system, in some degree at least, seems to be beyond question. Emotional and other nervous influences may markedly affect the output of milk. It appears to have been demonstrated quite conclusively, however, that the nervous element of control must be considered as of lesser importance than the endocrine, for after section of all nerve connections to the gland active milk secretion proceeds and the development of the glands is not appreciably affected. Some experiments, moreover, tend to show that even before parturition such severance of the nerves does not prevent mammary development nor interfere with normal lactation following delivery. The endocrine factor, therefore, appears to be controlling. Several tissues supplying an internal secretion are involved and various attempts to explain lactation through the medium of the internal secretions of the ovary, corpus luteum, pituitary, uterus, fetus, placenta, etc., have been made. The placenta doubtless contributes to—if it is not wholly responsible for—the mammary hyperplasia, the formation of the colostrum and the addition to the milk of a growth producing principle; this is indicated by Hammett's experiments.

Effect of Ingested Placenta on Lactation

Hammett records[5] remarkable results in breast-fed infants of mothers receiving desiccated placenta. The ingestion of placenta is attended by marked increase in the rate of growth of the infants. Not only is the decline in weight immediately following birth less, but the gain in weight in each case is greater day by day than that for the controls (mothers not receiving placenta). In his observations, on the thirteenth day the mean increase over the normal was 60%. This strong evidence of a growth promoting principle, secreted by the placenta and passed into the milk in feeding experiments and exerting definite and marked growth effects upon the infant, is indicative of the value of placental extracts in medicine. The evidence as to the actual increase of milk production following administration of placental preparations is not concordant. The evidence above would show it to be limited to the first stage of milk production only. Hammett was unable to find any increase in milk production in his series of placental fed women. However, Van Hoosen[6] found the following:

"1. Placental hormone in sixty-grain divided doses administered in six hours has no deleterious effects on the patient.

"2. Forty to sixty grains of the dried extract given in capsule form during the first six hours following delivery quickly stimulates the secretion of milk and the stimulation continues for three or four days.

"3. If forty to sixty grains are administered during or just before delivery, the milk appears on the first day.

"4. If administered immediately after delivery (during the first six hours), the milk appears on the second day.

"5. Painful congestion and turgescence of the breasts that often accompany the establishing of lactation is avoided by using placental hormone before, during or after delivery.

"6. Placental hormone will stimulate the secretion of milk at any period of lactation if given in four- or six-grain doses one hour apart and repeated every three or four days.

"7. The milk secretion which tends to decrease on the seventh or eighth day may be maintained or increased by repeating the post-partum dose on the sixth day.

"8. If placental hormone is given in five-grain doses three times a day for one or two weeks previous to delivery, the action of the post-partum dose is more effective."

The injection of extracts of corpus luteum and post-pituitary (Ott and Scott; Mackenzie) stimulates milk production and suggests an influence on normal physiological lactation.

The work of Eckles and Palmer[5] offers some explanation of the lactation process in general and of the part played by hormone control. These observers believe that there is both a nervous and a hormone element concerned. They believe that the chemical stimulus is the dominating factor in milk production immediately following birth and that the nervous mechanism of control gradually becomes more and more important as the chemical influence wanes. The chemical stimulus determines the maximum output of milk for the individual and is, to some extent, independent of nutrition. The phenomenon of lower animals eating the placenta immediately after the birth of the young has long been observed and is interesting in connection with the observations of Eckles and Palmer.

An interesting case, suggestive of the hormone element in lactation, is that of Rosa and Josepha Blazek. These sisters were structurally united throughout life and, although they had independent central nervous systems, they were joined by a common circulatory system. Following the pregnancy and birth of a child of one, there was lactation in the breasts of both.

Eclampsia

Numerous attempts have been made to relate eclampsia to some disturbance of the placenta. Theories have appeared attributing this condition to increased production of placental enzymes, the production of poisons by the placenta and numerous others. The research has pretty conclusively shown that eclampsia results from an accumulation of toxic protein

products of intermediary metabolism, which are ordinarily synthesized by the normal placenta into harmless metabolites for excretion. In eclampsia the function of the placenta is altered, so that this normal synthesis of toxic products into non-toxic is interfered with, and, coupled with this, there is apparently an increased placental permeability permitting the free passage into the maternal circulation of the toxic waste products of the fetus. In any event, eclampsia has not been shown to be related to the endocrine functions of the placenta.

THERAPEUTICS

The evidence of the hormone function of the placenta, in instituting the milk flow and in furnishing a definite growth promoting principle, is well established and the influence of the corpus luteum and pituitary on this function has been referred to. For clinical use, mammagen, a combination of placenta, corpus luteum, pituitary and mammary, has been found of the greatest value, and clinical reports of its use warrant the opinion that it is a very well-selected combination. The administration of mammagen should begin at least two days before delivery and be continued as long as the necessity therefor remains.

Other methods for re-establishing or maintaining lactation should not be ignored. The value of proper diet should constantly be borne in mind. A demand on the breast is most important and this may be accomplished by having the child put to the breast at regular intervals and allowed to nurse, even though there is no milk; or the breast is grasped with the fingers a little back of the areola and a milking motion carried out toward the nipples, the breast being pulled downward and forward. The action of mammagen may frequently be much aided by a proper attention to such procedures. Dose: 1 or 2 tablets or capsules three times daily after meals.

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PART II

CHAPTER IX

DUODENAL AND GASTRIC MUCOSA

In 1902 Bayliss and Starling demonstrated the internal secretion of the duodenum, and their work is regarded by many as the best demonstration ever made of internal secretion action. It had been shown (Pavlov) that the introduction of a dilute acid or acid chyme into the duodenum caused the secretion of the pancreatic juice, and this was presumed to take place through nervous pathways. Later it was shown by Popielski and Wertheimer, working independently, that the secretion of the pancreatic juice was stimulated by acid injection into the duodenum, even though all nervous pathways were severed—vagi and sympathetic ganglia.

Bayliss and Starling corroborated this work, which clearly indicated, if it did not conclusively prove, that the stimulus to the pancreas was mediated through the blood stream and not through nervous pathways. Inasmuch as injection of dilute acid into the blood stream failed to give any such effect, it was concluded that the addition of acid to the duodenal mucosa must give rise to the formation of some substance which is then absorbed and carried by the blood. To test this theory, they prepared from duodenal scrapings an acid extract which, when filtered and injected, caused a profuse flow of pancreatic juice.

These results have since been confirmed by many other observers and have led to the general acceptance of the idea, that in normal physiology the acid gastric contents upon entering the duodenum activate or convert a substance called prosecretin into the hormone named by Starling *secretin*, which is absorbed by the blood and electively stimulates the activity of the pancreas. In addition to stimulation of the pancreas, secretin in lesser degree stimulates the flow of bile [1] and of the intestinal juice. Downs and Eddy [2] also showed that, upon injection of secretin even in small doses, "it is possible to produce a considerable increase in the red corpuscle count per cubic millimeter of blood by the administration of secretin even in small doses and by subcutaneous injection." This increase was transient, but could be maintained for hours by frequent doses and disappeared after the last dose.

These results were confirmed by Fujimoto,[3] who also found an increase in the white cells and the catalase content of the blood. This effect of secretin in increasing the red and white cells is evident, not only by the injection of secretin but also by the increase which takes place during digestion. Downs and Eddy [4] found the following:

> "1. During digestion there occurs an increase in the number of both the red and white corpuscles per unit volume of blood.
>
> "2. These changes are comparable with the effects produced by the experimental administration of secretin.

"3. The source of the increased corpuscle content of the blood both in digestion and after the administration of secretin is an increased rate of production of new cells by the bone marrow.

"4. The similarity between the differential leucocyte counts in digestion and after the administration of secretin is additional evidence of secretin being the cause of the increase in the number of corpuscles during digestion."

They conclude from their investigation that the increase in white and red cells is due to a stimulation of both bone marrow and lymph glands by secretin.

The close similarity, if not identity, of secretin with antineuritic vitamin has been suggested by Voegtlin and Myers,[5] who found that an alcoholic extract of dried brewer's yeast, prepared in the same way as Funks' vitamin, causes on injection a marked increase in pancreatic secretion and flow of bile. This is not supported, however, by the conclusions of Downs and Eddy.[6]

Secretin can be obtained (Bayliss and Starling) in largest quantity from the duodenum. It is present in small quantity in the jejunum, hardly at all in the ileum, and is almost entirely absent in the salivary glands, liver, spleen, pancreas and kidneys. However, some observers have isolated it from other tissues of the body, although in small amounts. Luckhardt, Henn and Palmer[7] found that preparations obtained from the gastric mucosa were as active in stimulating the pancreas to activity as were secretin preparations made from the intestinal mucosa. This would impair the theory of the specific action of secretin and of gastrin (gastric secretin), especially since they found gastrin in the liver and thyroids as well.

Popielski explained the action of duodenal acid extracts on the basis of a vasodilator substance which caused stimulation of the nerve centers through anemia, and some authors have regarded the active principle as cholin, while others believe that it is very similar to histamin. It would appear from the experimental evidence, however, that it is a definite and distinct chemical compound. It is not a ferment. Secretin is probably formed as a result of the action of acid in the cells of the mucosa and absorbed from these. Trypsin and pepsin are said to destroy it. Bayliss and Starling have fairly well shown that the vasodilator principle is entirely distinct from secretin.

In 1906 an internal secretion, in many respects similar to secretin, was shown by Edkins to be present in the gastric mucosa. This is gastrin or gastric secretin. Edkins demonstrated that injections of an acid extract of pyloric mucosa caused a secretion of gastric juice. Extracts from the fundus failed to give these results. These experiments of Edkins have been successfully duplicated by others. As has been mentioned above, an origin of either duodenal or gastric secretin in a specific tissue has been seriously questioned.

Popielski has been the chief opponent of an explanation on the basis of a humoral action, and Lim[8] is also of the opinion that there is no

internal secretion in the blood after meals capable of exciting gastric secretion.

Ivy and Whitlow,[9] using the "two gastric pouch" method, failed to excite an increase of secretion in the "Pavlov pouch" when various substances, including foods, were introduced into the "pyloric" pouch. According to the gastrin theory, food substances should cause the formation of a hormone which would be absorbed and stimulate the secretion of the glands of the fundus. They state, "Our results do not support the gastrin theory." These experimenters avoided the sources of experimental error which made the work of Edkins subject to criticism.

While the evidence for a specific origin or a specific action of gastrin or secretin appears doubtful, and in the case of gastrin the whole theory seems uncertain, there is abundant evidence that secretin does act in a manner demanded by this theory. It also, in addition, appears to stimulate bile and intestinal juice and increase blood cells. A nervous mechanism, at the present time, however, cannot be wholly excluded. Starling recognizes this and says, "One must conclude that, although the nervous system may play a small part in the excitation of this gland, the main factor involved is the chemical mechanism which has just been described." Some authors have described differences in pancreatic secretion presumed to have been caused by these two different stimuli.

THERAPEUTICS

> "The chief action of duodenal organotherapy is to stimulate the action of secretin and re-enforce biliary, duodenal and pancreatic secretion and stimulate the contractions of the intestines."[10]

It is no argument against the therapeutic use of duodenal and gastric mucosa that the extracts obtained from them are not strictly specific. All experiments show that the effects in increasing pancreatic, gastric, intestinal and biliary secretion are well marked and positive. If, as has been said, there is any destructive effect of enzymes on secretin and gastrin in the digestive tract, the well-established therapeutic action is probably accomplished by a homostimulative action. Secretin may be preserved in desiccated form, and it seems likely must exert some direct action even if it is partially oxidized. For clinical use, secretogen and secretogen elixir have been found very satisfactory preparations.

Secretogen tablets contain prosecretin and enterokinase from the duodenum, combined with the proferments of the pancreas. Secretogen tablets promote the flow of the pancreatic juice, the bile and the intestinal juice. They aid digestion and favorably influence most cases of constipation. This effect is doubtless the result of the presence of a peristaltic hormone secreted in the walls of the intestine. Secretogen tablets are of the greatest value in cases of intestinal toxemia, and the various types of indigestion arising as a result of faulty pancreatic and intestinal secretion. The natural physiological stimulus of secretogen tablets permits their use over a long-continued period of time.

Dose: 1 to 3 tablets before or after meals.

Secretogen elixir is prepared from gastric secretin obtained from the pyloric antrum and pancreatic secretin from the duodenum, combined with the enzymes of the peptic glands, and 1/10 of 1% HCl. Secretogen elixir is a physiological stimulus to the secretions of the stomach, liver and pancreas, and if administered before meals stimulates both the appetite and digestion.

Elixir secretogen is indicated in atony of the stomach, dilatation, fermentative dyspepsia of the atonic type with gastrointestinal flatulence, chronic gastric catarrh of the asthenic type (that is, with the diminished HCl secretion) and in all cases where there is gastric insufficiency resulting in delayed emptying and consequent stagnation of the stomach contents.

Dose: 1 to 3 teaspoonfuls before or after meals.

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PART III

CHAPTER I

INTERNAL SECRETIONS IN GYNECOLOGY

To organotherapy must be given the credit of introducing into gynecology a system of medical treatment as opposed to surgical procedures which had grown and multiplied to such an extent that gynecology in the minds of many physicians came to mean a special branch of surgery. The diverse and apparently unrelated symptomatology encountered in gynecological practice defied explanation and made interpretation in terms of known physiological mechanism impossible. It is not difficult to believe that in the days gone-by the female of the species, with her infinite pains, aches and feelings, received somewhat scant sympathy from our profession, which may too often have regarded as whimsical and emotional these curious syndromes. Endocrinology, in its practical application as organotherapy, contributed more perhaps to gynecology than to any other branch of medicine. The early experimental work of Prenant, Bouin, Ancel, Fränkel, Born, Goltz and others demonstrated without question an endocrine action of the ovary and corpus luteum on menstruation and embryonic development. Further observations on the hypertrophy of the pituitary, thyroid and adrenal cortex during menstruation and pregnancy suggested a function of these glands in the phenomena which later gained general acceptance and contributed to the establishment of the general conception of endocrine interrelationship. With the development of knowledge of the interrelationship of the vegetative nervous system and the endocrine system, there became evident a mechanism sufficient to explain in large part the old, well-known syndromes of gynecology. Endocrine interpretation made organotherapy follow as the logical treatment.

Endocrine Factors and Sex Characteristics

The intimate relationship of the endocrines to the female organism is suggested by the generally accepted views of the influence of the sex glands on the development of the secondary sex characteristics. The embryonic origin of the sex apparatus is undifferentiated. In man about the fifth week the previously undifferentiated genital trace develops into the primary sex organs of one or the other sex. The Wölffian and Muellerian ducts develop up to about the third month of embryonic life without giving rise to the special characteristic morphology of either sex. About this time, differentiation takes place and there arise the special secondary sex organs of one or the other sex. The developing sex cells with their internal secretion influence in marked degree the further development of the organism.*

*This seems much more probable than that theory which holds that sexual dimorphism is a result of inherent influences from the very beginning — the primordial cell. This theory holds that not only are the sex cells differentiated, but the somatic cells as well. Such a method, however, very probably is operative in the lower orders.

Internal Secretions Determine the Sex Characteristics

In the female the ovarian hormones determine the development of the secondary sex characteristics and psychic and somatic peculiarities of the female—female type of mammae, skeleton, hair and fat distribution, voice, psyche, etc. "Woman is woman by reason of her generative glands. All the peculiarities of her body and mind, . . . everything in fact which in the true woman we admire and revere as woman, is dependent upon the ovary."[1]

The work of Steinach has rather firmly established such theory and gives suggestive evidence of the particular part of the sex glands responsible for these profound effects. In his work on male animals, he transplanted testes to other regions of the body. These animals underwent normal development, including the development of the secondary sex characteristics, with sex inclination and libido. On section, these transplanted glands showed atrophy of the spermatogenic elements and hypertrophy of the Leydig (interstitial) cells. If the animal was castrated without transplantation, the secondary sex characteristics and sex desire failed to develop. Steinach's later work in ligating and resecting the vas deferens, with a resulting atrophy or even disappearance of the sexual elements and increase in the interstitial cells, lends further proof that the elements exerting the hormone control are the interstitial cells. A name now familiar, "puberty gland," is applied to the cells taken as a whole. The homologous cells in the ovary are referred to simply as the interstitial cells. Further and even more striking evidence of the influence of these cells upon the development of the secondary sex characteristics is furnished by Steinach's experiments in transplanting ovaries into castrated males of the same species. Here there was a failure of development of the secondary male characteristics and the appearance of certain characteristics of the female — mammary glands' hair, etc.

The foregoing emphasizes the intimate relationship of the endocrine to the sex organs and characteristics of the female and the need for endocrine interpretation in the diagnosis of the disease conditions peculiar to the female genital apparatus. It may be added, as an aid to understanding some of the abnormalities of constitution and psyche, that irrespective of the course of this differentiation — that is, whether male or female — there remains always some remnant of the opposite sex. Thus in the female the Muellerian duct develops into the oviducts, uterus and vagina and the Wölffian duct largely disappears. However, part of it persists as the parovarium, the homologue of the epididymis in the male. Moreover, in pseudohermaphroditism both the Muellerian and Wölffian ducts may develop and give well developed secondary sex organs (ducts, external genitalia, etc.) of both sexes in the same individual Thus, while in general the primary sex cells determine the character and development of the somatic tissues and secondary sex characteristics certain exceptional forms of development may take place.

Striking Changes of Puberty are Endocrine Effects

At puberty equally striking endocrine effects appear. The phenomena of ovulation, menstruation and pregnancy are inseparably bound up with the internal secretion of the ovary and corpus luteum and are perhaps equally dependent, if not so directly, upon the thyroid, the pituitary and the adrenals. The relation of the ovaries to menstruation was one of the first to be investigated and the results of such research leave no doubt as to the causal relationship. Following the removal of both ovaries there is complete cessation of menstruation, which may be reestablished by grafting an ovary under the skin or in other favorable sites in the body. The further removal of this transplant will again cause cessation of the menses. Such experiments seem effectually to disprove the intervention of a nervous mechanism such as required by Pflüger.

In normal physiology menstruation makes its appearance at the beginning of the period of sexual maturity. In temperate climates, with exceptions for individual and racial variations, this maturity is reached at about the age of fourteen or fifteen years, and menstruation continues as a periodic phenomenon until the time of the menopause—usually from forty-five to fifty years of age. The usual interval elapsing between the menstrual periods is approximately twenty-eight days, but variations from this figure are encountered with such constancy that menstruation occurring at intervals of from twenty to thirty-five days may usually be regarded as normal and as not requiring treatment. The period of menstruation is attended by marked changes in the emotional and physical constitution of the woman. Concurrently with the well defined histologic changes occurring in the uterus itself and the "hyperemic wave," which affects not only the uterus, ovary and genitalia but in some degree the whole body, there is definite approach to the maximum of metabolic activity, culminating at the beginning of menstruation and subsiding thereafter. Of the emotional symptoms, the tendency to irritability, lack of self-control, unreasoning attitude and lack of poise is well-known and varies greatly in normal women. In states of abnormal psychology and definite mental and nervous disease the emotional symptoms are intensified. Amenorrhea, the absence of menstruation or menstruation at very irregular periods, is frequently met with in medical practice and demands careful diagnosis and appropriate therapy.

Normally at from forty-five to fifty years of age menstruation ceases and the active sexual life of the individual ends. The ovary is the organ of internal secretion directly connected with menstruation and the premenstrual uterine changes, including the development of the uterus. The effects of the thyroid, pituitary and adrenal cortex are no less certain but are less direct. The results of the removal and transplantation of the ovaries on menstruation have been mentioned. Such removal in the very young animal, before puberty, results in failure of development of the uterus. The exact relations existing between the ovaries and the menstrual phenomenon have been the subject of much speculation. Two theories are worthy of consideration here:

Relation of the Ovaries to Menstruation

1. The explanation offered by Biedl that the interstitial tissue of the ovary furnishes the internal secretion responsible for the characteristic histologic changes of menstruation and of oestrus. In this theory the internal secretion of the interstitial cells is functionally active in the nidation and the development of the ovum after fertilization. A functional antagonism between the interstitial stroma cells and the sex cells is assumed and explains the hypertrophy of the interstitial and atrophy of the remainder during menstruation and pregnancy. This hypertrophy and hypersecretion of the interstitial cells depresses the secretion of the rest of the ovary and accounts for the evidences of ovarian insufficiency at these periods. The theory seems in conflict with generally accepted views at one point, as it assigns to the interstitial cells a function in the local menstrual and reproductive processes only and not in connection with the more profound processes of somatic growth and development.

2. The second hypothesis as to the relations of the ovaries and menstruation is usually referred to as Fränkel's hypothesis. Fränkel assumes that the corpus luteum is the active determining factor in menstruation and the premenstrual uterine changes. Such a relationship had previously been suggested by Born. Fränkel assumes that ovulation takes place about two weeks before menstruation and the resulting corpus luteum furnishes the hormone which sensitizes the uterus and causes the uterine changes characteristic of the premenstrual period. Fränkel's theory, however, is not generally accepted and much evidence at hand tends to disprove it. Ovulation and menstruation frequently occur at times bearing no fixed relation to each other and menstruation may occur independently or without ovulation.

Cyclic changes in the uterus and perhaps other structures of the body undoubtedly take place at the menstrual period, which have been described as premenstrual waves of hyperemia (Dalché). This cyclic phenomenon or tendency may be independent of any effect from the ovary. It is found in lower animals in which the reproductive function is limited to seasonal periods (oestrus) and in which the physical and histological changes both correspond very closely to those in the human female during and before menstruation. In primitive races, there is a resemblance to this lower order condition, for in them there are discernible traces of a tendency to sexual seasons and the period of the menses differs from the usual type. In some, menstruation takes place in one part of the year only.

Frank summarizes the theoretical relation between the ovary and corpus luteum and menstruation as follows:

1. Full maturation of follicles causes the premenstrual changes.
2. Follicular rupture coincides with or follows closely the onset of the menstrual flow.
3. During the active growth of the corpus luteum
   (a) The uterine mucosa is sensitized, so as to be capable of receiving a fertilized ovum;
   (b) Follicle ripening is interfered with.
4. During pregnancy the corpus luteum persists; follicular ripening is, therefore, interfered with and hence the menstrual cycle is postponed.

As evidence of the action of the corpus luteum in sensitizing the uterine mucosa and retarding ovulation or the ripening of the follicles, Frank refers to the convincing work of Leo Loeb, who demonstrated in animals that "the uterine mucosa reacts to trauma (foreign bodies, ovum) by producing a decidua which far exceeds in volume the spontaneous oestrual or menstrual decidua (experimental deciduomata). If the corpus luteum is destroyed or removed, neither the normal nor artificial decidual reaction takes place; therefore, the ovum cannot be embedded." Loeb found in 66 guinea pigs that spontaneous ovulation rarely occurs within 16 days after a preceding ovulation. In 25 animals all the corpora lutea were successfully removed and in 92% of these ovulation occurred within twelve days after coitus, showing a marked shortening of the interval between ovulations. The presence of a corpus luteum or the injection of corpus luteum extracts into fowls prevents ovulation.

AMENORRHEA

"It is a very great mistake to treat amenorrhea as though it were simply a lack of menstruation, for it is a great deal more than that. Behind this lack lies a cause. It may be in the uterus or the ovaries or it may be still further back in the secretion of the endocrine glands or in the functioning of the vegetative nervous system."[2] The importance of the endocrines in normal menstruation has been described. It should not be assumed, however, that organotherapy is the sole method of treatment or that it is even the method of choice in some cases. Structural defect and emotional influences obviously demand treatment specifically directed to these causes. Amenorrhea as a result of emotional disturbance is not uncommon and even here the endocrine system may be an intermediary if not a causative agent. Christides[2] in an article on "Hysterical Amenorrhea" describes such types, and states that in these cases the gynecological condition is improved by recovery from the nervous states. Often there is increased irritability before menstruation, states of anxiety and semi-hysteria. In the greater number of cases of functional amenorrhea an endocrine basis may be demonstrated. In the menstruation phenomenon the ovary is the endocrine gland immediately concerned but the influence of others, particularly the thyroid and pituitary, should not be overlooked either in diagnosis or therapy. The three *demonstrable* endocrine types are the thyroid, pituitary and ovarian. Engelbach[11] illustrates these three types of endocrine menstrual deficiency as follows. They may be studied as type cases of these general classes of amenorrhea.

Endocrine Types of Amenorrhea

Pituitary Type: The pituitary patient had never menstruated. At thirteen she ceased to grow and her facies, bodily contour and lack of secondary sex characteristics remained those of a girl just approaching puberty. Her head was too large for her body and its circumferences not proportioned to one another. From vertex to symphysis she measured two inches shorter than from symphysis to soles of feet. Her height was four inches less than her span. The upper incisors were large and the adjoining canines small. The sella turcica was normal, bones slender, there were no adipose deposits, the thyroid was slightly full.

Ovarian Type: The ovarian patient menstruated regularly and painlessly from thirteen to seventeen. At that age she was suddenly seized with diffuse abdominal pain, tenderness centering at McBurney's point and repeated spells of vomiting, since which she has never menstruated. Removal of the appendix failed to give relief and attacks of migraine with visual disturbances were added to her symptoms; also attacks of sudden edema, dyspnea on exertion and acne of face and chest. She was poorly nourished, tall and slender. Periostitis existed in the right ilium, right femur and both tibia and arthritis in the right sacroiliac joint, accounted for by a 2-plus Wassermann. Luetic treatment for about a year caused the reaction to become negative but during this period her emaciation, abdominal pain, iliac and sacroiliac tenderness, amenorrhea, headaches and vomiting had continued and grown steadily worse. An exploratory operation brought to light no abdominal abnormality and no adhesions. From this time on she was given a daily injection of corpus luteum extract and 10 grains of the same preparation by mouth after each meal. Improvement of all symptoms began at once and continued during three years under observation, but menstruation was not restored.

Thyroid Type: The thyroid patient menstruated normally from eleven to fourteen, then began to have irregular attacks of amenorrhea, alternating with normal menstruation. She complained of feeling weak and exhausted, of weak eyesight, of intermittent coccygeal pain and of ecchymotic spots frequently appearing on various parts of her body. She had rickets when a baby and now her upper incisors are large and her upper canines small. She is short of stature and spans some inches more than her height. Her hands and wrists are slender, the epiphyses of radius and ulna not joined to the shafts. Her forehead is low, eyes squinting and deep set, nose of saddle shape with point retroussé, lower teeth crowded a little. No obesity, but breasts, abdomen and mons veneris normally developed; hair in axilla and on mons. Temperament phlegmatic. Thyroid enlarged; sella turcica large.

Engelbach first directs attention to the early personal history of these patients. In pituitary and thyroid disturbances it has little significance, but suspicion of prenatal thyroid deficiency should be aroused by a size exceeding ten pounds at birth, by delayed healing of the navel, late eruption of the teeth and deferred walking and talking; also in defective children and those backward at school. Many cases of rickets have been treated with mechanical appliances by competent orthopedists without suspicion of an underlying thyroid cause for the lesion. It is the rule that the hypothyroid girl menstruates at a much earlier age than the normal;* there is a tendency to increase in duration and amount of the flow but without dysmenorrhea. The periods of the eunuchoid girl usually appear after the age of fourteen, are more scanty, of shorter duration and accompanied by more or less dysmenorrhea. The distress, being often located over McBurney's point, is apt to lead to a diagnosis of appendicitis. Nausea, vomiting, backache and extreme malaise are frequent, as they also are with hyperthyroidism.

*(This statement has been questioned.)

Individuals of the pituitary type never mature at all or, if they do, late in adult life. In milder cases, the menses may occur at normal intervals but are imperfect in duration and amount and frequently associated with more or less dysmenorrhea and migraine. The history of the eunuchoid type consists in menses that come on after the fourteenth year and are fairly normal at first, gradually decreasing in duration, amount and regularity, accompanied by increasingly severe dysmenorrhea.

In hypopituitary cases there is found an infantile genital tract and absence of secondary sex characteristics. In the eunuchoid the genitals and sex characteristics are properly developed. Thyroid cases usually display a very early overdevelopment in these respects. Insufficiency of ovarian secretion, by withholding the natural antagonist of pituitary and thyroid, permits these latter to cause an overgrowth of the long bones, as seen in the eunuchoid girl. In the other two types this does not occur and consequently there is produced a very short stocky individual. Normally the measurements from symphysis upward and from symphysis downward should be equal. In Engelbach's ovarian case the latter exceeded the former by three inches, the span was the same as the height, although it should have been but double the upper measurement. In the pituitary individual, if disproportion occurs, the upper measurement exceeds the lower.

To a girl whose basal metabolism is thirty per cent. or more below normal, Engelbach gives some preparation containing the equivalent of one-fourth of a grain of extract of whole thyroid three times a day, increasing the dose by one-fourth of a grain each week until the first signs of intoxication appear. Tachycardia above 100 is likely to be the first such indication and the dose which produces it is then slightly decreased and continued for some months until relief is obtained. The ovarian dose must be experimentally ascertained for each individual, beginning at five grains of solid extract and one cubic centimeter of fluid corpus luteum. Stroma and corpus in his experience have proved about equally effective in relieving eunuchoid amenorrhea. Engelbach found hypodermatic administration valuable in both pituitary and ovarian types of cases.

The amenorrhea of puberty is of a different type from those described by Engelbach. In these cases there is usually involvement of ovaries, pituitary and thyroid and treatment with this combination of gland substances is usually effective. Of this type, Dalché says[2] "The amenorrhea of puberty should not be allowed to go on indefinitely because the sooner it is overcome the easier it is to correct the underlying faults. The fault is lack of stimuli to the ovaries from the thyroid and pituitary, but in some cases these fail even with the ovaries added and it is strange but secretion of the prostate and testicles will sometimes prove efficient when these others fail."

Organotherapy in Amenorrhea Usually Successful

Treatment: The determination of the glandular type of the amenorrhea is important and is valuable in determining the treatment. While it is true that practically all cases respond better to pluriglandular combinations of ovary, pituitary and thyroid, the diagnosis of predominating fault in any individual gland suggests supplementing the therapy by additional dosage of this particular gland sub-

stance. In many instances, as found by Engelbach, hypodermatic administration forms a valuable supplementary treatment. The time element in the treatment of amenorrhea is important, in view of the cyclic elements in menstruation. The maximum therapeutic effort ordinarily should be made just before the estimated time of the menstrual period, in order to take advantage of the combined results of both the therapeutic agent and the cyclic premenstrual changes.

Summary of Treatment:

1. For routine treatment of functional amenorrhea without predominance of symptoms of a particular gland, Hormotone (thyroid-pituitary-gonad formula) should be given in a dosage of 1 or 2 tablets three times daily. The synergism existing between these gland substances is one of the established facts in organotherapy.

2. When predominance of symptoms points to a well marked gland type, such as described by Engelbach, — ovarian, pituitary or thyroid — use Hormotone in a dosage of 1 or 2 tablets three times daily, supplemented by a minimal dosage of the particular gland substance, which may be increased to full therapeutic dosage, to be determined in each case. The desirability of combined gland therapy is recognized by Graves in describing the pituitary type of case:

> "In gynecological practice extracts of the whole gland are indicated in menstrual disorders that are essentially the result of pituitary deficiency, in which cases ovarian therapy may be used in combination."

3. In some cases it may be necessary to resort to hypodermatic administration of corpus luteum, solution of posterior pituitary, etc., as supplementary treatment to Hormotone.

DYSMENORRHEA

Dysmenorrhea an Endocrine Disease

Dysmenorrhea is painful menstruation occurring at the time of the menstrual period and distinguished from oozing, bleeding and abnormal uterine conditions characterized by pain during the interval between the periods. As a definite disease, dysmenorrhea may be regarded as an endocrine disease, for in those gynecological conditions such as malposition of the uterus, elongated cervix, uterine structural changes, etc., dysmenorrhea is a term descriptive of a symptom, pain, rather than a disease itself. In considering the etiology of dysmenorrhea the various structural or mechanical defects should first be considered. In those cases of determinable defect such as malposition of the uterus, anteflexion, faulty development of the uterus, etc., surgery is indicated. It seems certain, also, that, although dysmenorrhea is no longer believed in most cases to result from damming back of menstrual blood as a result of stenosed, infantile, cicatricial or flexed cervix, these causes are active in a sufficient number of cases to warrant an examination especially for them before attempting treatment by organotherapy. Operative procedures in cases of these structural abnormalities are usually sufficient to afford relief from the pain. Aside from all these conditions of malposition, infantile uterine development, etc., there remains

that large class of cases of dysmenorrhea in which such defects are not present, and in which the cause must be sought for in the functional mechanism of the menstruation process.

The character of the pain in dysmenorrhea is suggestive of the underlying pathologic condition — a spastic, intense contraction of the uterus. This condition seems to prevail uniformly in the several types of dysmenorrhea, regardless of the cause. The pains may be of short duration or persist throughout the menstrual period. They are cramp-like, frequently accompanied by desire to flex the thighs on the abdomen, and accompanied by emotional disturbances which may be severe. These psychic disturbances incident to menstruation may become greatly aggravated. The mental condition is one of unrest and apprehension. Vomiting, headache and anorexia are common.

Before assigning endocrine dysfunction as an etiological factor in these cases some mention should be made of the neurogenic theories of the cause of dysmenorrhea. Various attempts have been made to explain the condition by excessive irritability of the uterus, by nervous stimuli and as a psychoneurosis. There has been a lack of general acceptance of any such views and a marked tendency to an endocrine explanation. It is not improbable that the endocrine factor involving several of the associated endocrine glands may also involve the nervous system. The intimate relationship between the vegetative system and the endocrines suggests such a possibility, although it is uncertain whether the primary causative factor is in the vegetative nervous system or in the organs of internal secretion. The character of the symptoms of dysmenorrhea strongly suggests that both these causes are associated in the condition. Treatment by organotherapy by its successful results suggests that the endocrine defect is primary.

Striking Success of Pluriglandular Therapy

Treatment: Those cases with anatomic defect, malposition, stenosed cervix, etc., require appropriate surgical intervention, the result of which is usually good. In the endocrine cases pluriglandular therapy has been remarkably successful. To the ordinary dosage of thyroid and pituitary, ovarian substance in much larger dosage may be added. The value of ovarian therapy in these cases is especially good and the statement of Graves is typical of the experience of a large part of the profession:

> "The author has recently had striking success in a number of dysmenorrhea cases with a preparation of desiccated ovaries of pregnant animals, minus the corpus luteum. The most marked effect of the extract is seen in its influence on the headache, nausea and vomiting from which many dysmenorrhea patients suffer."

Graves has had marked success in the use of ovarian residue and with extracts of the entire ovary and notes that his results compare favorably with those of physicians who have used the corpus luteum preparations.

In a meeting of the Section of Obstetrics and Gynecology, of The Royal Society of Medicine, held on June 7, 1923, a paper was presented by Leonard Phillips, M. S., M. B., B. Sc. Lond., F. R. C. S., Eng., on the

treatment of 100 cases of dysmenorrhoea. The paper is valuable not only for its practical suggestions as to treatment, but also for the very simple and practical clinical types of dysmenorrhoea which are outlined.

Fifty of the cases were treated by organotherapy, either alone or in combination, and it is interesting to note that forty-six of the fifty cases so treated were relieved. In the study of these cases there was an attempt made to outline types and relate treatment thereto. The following general facts were noted in these cases: Practically all of the patients were engaged in sedentary occupations. Most of them were single and gave a history of menstrual disturbance. One class of cases gave a history of menorrhagia associated with failure of development of the sex organs. Patients suffering from organic diseases were excluded from the series. The general appearance of these patients was one of muscular underdevelopment, faulty posture and breathing, visceroptosis, anaemia, etc. Headache, nausea, vomiting, diarrhea and frequency of micturition were common. The four types outlined were as follows:

Clinical Type 1. "Dysmenorrhoea is frequently a disease of faulty hygiene, upbringing and surroundings. A large proportion of these patients conformed to this definite type. They were thin, anaemic subjects, poorly developed, with weak abdominal muscles, absent abdominal breathing and faulty posture; they were constipated, had visceroptosis or a bad circulation, and followed sedentary lives with little exercise and fresh air. Naturally in such cases the uterus is often arrested in its development, and has a feeble musculature easily exhausted if given much expulsive work to do. An exhausted muscle forced to continue contractions gives rise to cramps and colicky pain, true alike of the heart, the gastrocnemius and the uterus. Constipation necessarily has a bad influence, for a mass of faeces in the pelvis acts very much as a pelvic tumour, increasing congestion."

Clinical Type 2. "There is a type of dysmenorrhoea case in which the disturbance is functional and allied somewhat to migraine. In addition to menstrual pain these women complain of general rather than local symptoms. Headache and nausea are common accompaniments of the pain. They are frequently sensitive, nervous, worried women with eye-strain and constipation, and the dysmenorrhoea is one symptom in a complex which Freud would have designated as the expression of an unsatisfied desire, and which lately has been described as an anxiety-neurosis. Whenever the general symptoms are more marked than the local, general treatment is more likely to be successful."

Clinical Type 3. "There is a third type of case in which the symptoms and signs suggest some form of obstruction as the chief causal factor."

Clinical Type 4. "There is a type of patient who complains of pain in one or other iliac region either alone or before the central pain, and in whom there exist *signs of arrested development of the genital organs.* Menorrhagia is just as common as scanty flow, because an undeveloped endometrium and musculature are linked up with a normal ovarian stimulus. Often there is nothing in the history to suggest obstruction, and clots may be absent. The obvious treatment in such cases is to stimulate development of the uterus, and this is often successful in abolishing the pain."

Fifty cases were treated with ductless glands, either alone or in combination with anti-spasmodics. Ovarian Extract, Corpus Luteum, Thyroid, anterior lobe of Pituitary, mixed glands and Hormotone were used. In speaking of Hormotone, the author says: "Why the latter should have proved the most valuable in this series of cases it is difficult to say. It consists of extracts of ovary, thyroid, pituitary and testis. We know that hypo-thyroidism, hypo-pituitarism, and hypo-oophorism may all be associated with pelvic hypoplasia, a condition observed in one-half of the cases in this series. It may be that in a 'Gatling gun' prescription such as Hormotone, containing all three extracts, one extract may hit the mark where the others fail. By estimating the basal metabolism rate it is possible to ascertain the existence of hypo-thyroidism even in the absence of clinical signs, but moderate ovarian and pituitary deficiency may be more difficult to determine, and herein lies the value of combined extracts. It is interesting to speculate upon a possible part played by the extract of testis, for this extract alone or in combination with extract of prostate is sometimes successful in dysmenorrhoea cases."

For purposes of comparison, a series of 100 cases were treated by operation, and it was found that 25% were cured, 25% relieved and 50% unaffected. These results were certainly much inferior to those treated medically, and should dictate some reserve in promptly resorting to surgical treatment.

General hygienic treatment, establishment of a correct mental attitude, correct clothing, correction of constipation and exercise are described as a part of the treatment, and in the discussion of the paper which followed the meeting these measures received endorsement. The hypothesis for the explanation of the observed superiority of Hormotone over other gland products and combinations may be correct, but the probable reason would appear to be that Hormotone furnishes an ideal combination of gland products, the potency of each one of which is certain, the combined effect of which is greater than the sum of the individual gland effects. The explanation of Blair Bell would appear to apply here:

"It is possible that the reason why physiologically active secretions of the various organs, such as the ovary, the suprarenal cortex and the anterior lobe of the pituitary, have not been obtained and utilized therapeutically is because they would not produce their effects single handed; they must either be activated by or combined with some other substance, as they are normally in the body, before they can give effect to any properties they may possess."

It may also be important that Hormotone contains extract of testis, for, as Dr. Phillips states, this extract alone is sometimes successful in dysmenorrhoea cases. The conspicuous success of this treatment commends it to every practitioner.

Summary of Treatment: Organotherapeutic treatment by means of thyroid, pituitary and gonadal substance is usually effective. The dosage of the ovarian substance — whole ovary, corpus luteum or ovarian residue — may be relatively larger than that of the others. Hormotone should be given in a dosage of 1 or 2 tablets three times daily and may be supplemented by 1 tablet of Ovarian Comp. t. i. d. or by one 5-grain tablet of corpus luteum, whole ovary or ovarian residue.

MENORRHAGIA

Practically all Menorrhagias Due to Disturbances of the Internal Secretions

Prolonged or excessive menstruation is termed menorrhagia. It is descriptive of abnormal alteration of menstruation and refers to a condition occurring at the menstrual period, thus differing from metrorrhagia, which refers to loss of blood from the uterus independent of the menstrual process or period. The quantity of blood lost varies largely with individuals and the presence of symptoms such as excessive prostration, anemia, etc., may serve to classify a flow as menorrhagia in one individual that in another would constitute a normal menstruation. Menorrhagia may be due to structural defects, uterine fibroid, pelvic congestion, etc., but its underlying pathology is usually endocrine. The particular site of the endocrine defect is not established with certainty although the ovary appears in all theories to be regarded as a prominent factor. Some authorities have attributed to other glands of internal secretion a very prominent part, but in all theories the immediate effect of ovarian dysfunction is recognized. Meyer-Ruegg[3] expresses a view which, in one form or another, is widely held. Without clearly defining the etiologic factors, this theory holds in general that causation is complex and due to involvement of several of the structures concerned, at the same time clearly recognizing the importance of the ovary as an intermediate factor. In discussing menstruation, its causes and abnormalities, he says:

> "It is not at all probable that these changes originate in the ovaries and it is much more probable that they are in consequence of the reciprocal relationship between the other glands of internal secretion, including the mucous membrane of the uterus and nervous system. That the disappearance of menstruation is directly due to changes in the ovaries is improbable because these changes are inconstant on the part of the ovary and because hemorrhages occur either with or without them, and because these same changes exist in the ovaries with or without hemorrhages. Furthermore, we are not sufficiently informed concerning the microscopic anatomy of the ovary during the different phases of its activity to enable us to determine what are physiologic and what are pathologic conditions. The same is true of the mucosa of the uterus. In the ovary we have a very important center which may be regarded as a relay station for influencing the processes in the uterus, and yet to explain uterine hemorrhages and more particularly to explain the arrest of bleeding we must chiefly refer them to local conditions, that is to say, to the mucosa itself."

Graves places greater emphasis upon the ovary as the causative factor and this appears to be the prevailing opinion. Graebke has pointed out that although the hemorrhages of puberty and the climacteric have been attributed to the ovary it is only recently that the hemorrhages which occur in the period of active sexual life have been explained in this way. Former explanations have included metritis, endometritis,

hemorrhagic hypertrophy of the glandular mucosa, etc. The influence of the ovary was made evident by the work of Hitschmann and Adler, who demonstrated that the hypertrophy of the uterine mucosa, which had been regarded as pathologic, was a normal premenstrual condition and that both normal and pathologic changes in the uterine mucosa and typical and atypical menstrual hemorrhages were of ovarian origin. The evidence seems clear that the ovary is a most important factor in these conditions, and that the ovarian dysfunction may be either primary or secondary to primary defects in the thyroid or pituitary. Graves says:

> "It is not at all unlikely that the menstrual disorders of the climacteric as well as those of the menarche are the result of irregularities in the hormones of the ovaries. It is thought by some that practically all menorrhagias are caused ultimately by a disturbance of the internal secretion of the ovary, and there is much evidence that this is true."

Treatment: Hormotone in a dosage of 1 tablet three times daily may be used for a regulatory influence. The restoration of normal function in the thyroid and pituitary may remove the condition. In cases manifestly of thyroid or hypophyseal origin, these extracts may act promptly in controlling the flow, and as a rule should be given as supplementary dosage to Hormotone. Mammary extract and pituitary substance are both of value by reason of their pharmacological action on the uterus and for this purpose may be used as supplementary treatment. Thymus substance has also been used for this purpose, but its uses are not as well established and its action certainly not comparable with mammary. Osborne says:

> "The only use for extracts of the mammary gland is in the profuse menstruation of young girls and young women, and in menorrhagia occurring at the time of the menopause, in other words, in functional bleeding. If there is a local organic reason for the increased flow, of course, it should be treated by proper local methods, but when a young girl floods, or menstruates every two or three weeks, and profusely, mammary tablets, two or three a day, beginning one week before the expected period, will very frequently postpone the period to the normal time. It is also advisable to begin on the third day of a profuse menstruation and give the girl three or four tablets a day, which will often shorten the period. Menorrhagia at the menopause may be stopped in the same manner."[4]

Such treatment by mammary and pituitary extracts, however, is symptomatic and should be used as adjuvant treatment to organotherapy by Hormotone or Hormotone and ovarian substance, which attempts to correct the underlying endocrine defect. For such purposes Mammary Comp. in a dosage of 1 or 2 tablets t. i. d. may supplement Hormotone.

METRORRHAGIA

Metrorrhagia is a term descriptive of loss of blood from the uterus in the intermenstrual period. It has no relation to the bleeding of the menstruation process and may be due to tumors, cancer, disease of the

endometrium and similar causes. Careful physical examination should always be made in metrorrhagia to determine the local cause. The treatment is surgical and in those cases with etiology similar to menorrhagia the treatment is the same. The symptomatic treatment is by means of mammary and pituitary substance. Mammary Comp. in a dosage of 1 or 2 tablets three times daily should be administered.

MENOPAUSE

The Menopause a Critical Period of Readjustment Involving the Endocrine System

At an age of from forty-five to fifty-five years the active sexual life of a woman comes to an end. Menstruation ceases and the metabolism, habits and psyche undergo changes varying with the individual. The menopause or climacteric is not a sudden transition from one state to another. Only in the most exceptional cases does menstruation end definitely, finally and abruptly. Usually the flow at the periods becomes progressively more scanty, the character of the blood changes and after a somewhat extended period of irregular abnormal menstruation the flow finally ceases.

The menopause includes much more than mere cessation of menstruation or the immediate changes connected with it. A comprehensive study includes consideration of the metabolism, psychic and mental changes and readjustment extending over a long period of the woman's life — a period characterized by Marañón as "the critical age:"

> "The menopause is not merely a syndrome of genital insufficiency as we believed until recently, but the biological and clinical consequence of a complex and immutable endocrine condition as is that of puberty, the glandular factors of which can be determined with some degree of exactitude, and this fuller knowledge of the mechanism of the condition allows us to explain clearly and to deal accurately with many details of the phenomenon of the climacteric that formerly appeared to us to be full of uncertainty. From this viewpoint, the classical concept of the menopause as a simple genital condition in women has disappeared and in its place there arises a much more comprehensive concept of the critical age — that is, of a long period of the life of both sexes, the principal factor in which is the genital apparatus, but in the development of which all the organic activities play a part."

The menopause may be a period of tranquillity, but undoubtedly the greater number of women experience some disturbances which require the attention of the physician. Hot flushes, vasomotor symptoms, dizziness, emotional disturbances and even well marked psychoses may be encountered. The central gland element in the changes of the menopause is undoubtedly the ovary, but it is certain that the associated glands by their reciprocal action largely influence the clinical picture. The relationship of the ovary with these associated glands, which are principally, at least, the thyroid, adrenal and pituitary, has been firmly

established, and it is not difficult to assume that at a period in which the action of one essential member of this associated group is removed there will be a consequent and determinable alteration in the functional activities of the remaining members of the group. As a matter of fact, many of the signs and symptoms of the menopause are referable directly to glands other than the ovary. One class of symptoms (vasomotor) of the menopause is so conspicuous that it has been held by many writers that almost all abnormal changes of the menopause may be explained in terms of such disturbance. Culbertson[5] studied the condition from this viewpoint. He conceives the menopause to be a functional disturbance of the endocrine system dependent upon the withdrawal of the ovarian secretion. Vasomotor disturbances are characterized by an instability of arterial tension and usually this appears as a "vacillating hypertension both systolic and diastolic." The hypertension is assumed to be due to a relative predominance of the hypophysis or the adrenals. The diastolic pressure is not increased to the same extent as the systolic, and the resulting larger pulse pressure is the immediate cause of the symptoms associated with the vacillating arterial pressure. The psychic symptoms appear to be most closely related to change in thyroid function and in the majority of cases hyperthyroidism takes place. The effect of organotherapy in reducing the blood pressure is taken as evidence that the hypertension is functional and not due to structural changes in the body. Such findings as those of Culbertson are found with the greatest frequency in the literature, and it seems beyond question that a large part of the clinical picture of the menopause is due to the predominance of the adrenal effects in raising blood pressure — effects which are in part due to the hypophysis and thyroid, and result from the withdrawal of the inhibiting effect of the ovarian secretion.

Vasomotor Symptoms Due to Adrenal Predominance

The views of the relationship of the ovary to the menopause held by Marañón are worthy of consideration here. He is not in agreement with the theory that the ovary is the primary internal secretory organ at fault at this time but believes that the changes in the ovary are preceded by changes in the other endocrine glands.

> "The continuous changes in the activity of the various endocrine glands in the course of life, which prepare the way for a certain event which may occur spontaneously or may supervene in consequence of the occurrence of other and external causes (emotions, various diseases, etc.), are the beginning of the functional decay of the ovary."

As an additional factor in increasing the blood pressure, Marañón includes withdrawal of the hypotensive effect of the ovarian secretion. Such an effect of the ovary he regards as conclusively proved and the combined action of these two factors, gradual withdrawal of the hypotensive action of the ovary and relative increase of the adrenal activity, account for the increased vascular tension and particularly for the unusual variations in pressure, the variability resulting because neither of the two actions is developed uniformly or at a fixed rate. The supra-

renal influence he regards as the more important of the two and as of early development in the menopausal condition.

As noted by Culbertson, Marañón, Zondek and others, the characteristic vasomotor disturbance of the menopause is not simple uniform hypertension, but a condition of vasomotor instability. The following summarization of Zondek's views[6] is descriptive of the whole series of vasomotor changes and their relation to the symptomatology: In the climacteric the vascular nervous system is exceedingly unstable. The vasomotor center is in a state of constant irritability. This irritability of the vasomotor center is caused by disturbances in the internal secretions of the ovaries and manifests itself by waves of vasodilatation and pathological distribution of the blood. These waves are characterized by (1) their paroxysmal occurrence, (2) by an initial disturbance in the rhythm of respiration, (3) by a pathological division of the blood. These waves are initiated by an abnormal impulse from the vasomotor center acting upon the vascular district supplied by the splanchnic, causing active constriction of the vessels in this district and driving great quantities of blood into the peripheral vessels. Active dilatation of these peripheral vessels may assist this distribution. The impulses follow each other in rapid succession so that the individual vasomotor effects are not fully developed. As suddenly as they were initiated, so suddenly do they cease, some other impulse taking the place of this one. Then the vasomotor center withdraws the blood from its stasis in the peripheral vessels by active dilatation of the splanchnic vessels, and consequent suction which is supported by vasomotor constriction of the peripheral vessels. Small wonder that these periodic surging waves of vasodilatation and constriction should cause distressing subjective sensations, syncope, palpitation, sweating and states of anxiety and fear. In cerebral efforts the vasomotor center reacts pathologically so that the blood supply so necessary for mental and psychical efforts is not regulated in a physiological manner but abnormally, much as it is in exhaustion or diseases of the nervous system. Physical efforts have a much more normal blood supply. The vasomotor center for heat regulation is frequently abnormal, it does not function in a physiological manner. As a rule, there is a paradoxical reaction to cold.

Internal Secretions and Vegetative Nervous System in Disturbances of Menopause

One other essential factor should receive consideration — the relationship of the vegetative nervous system to those abnormalities other than the vasomotor. In normal individuals the great divisions of the vegetative nervous system — the sympathetic and parasympathetic — are in a state of balanced equilibrium. Their actions are very largely mutually antagonistic and by the nicety of their adjustment afford a mechanism for the regulation of the functional activity of the organs and tissues innervated. The activities of the vegetative nervous system are influenced by the internal secretions and the organs of internal secretion are themselves influenced by the vegetative nervous system. The activities of these two are so intimately connected that disturbance in one must result in disturbance in the other. Now the vegetative nervous system and the endocrine

organs are active in the regulation of the functional activity of the vegetative processes of the body, so that the readjustment period is conceivably one in which there will arise not only vasomotor symptoms, but very diverse symptoms referable to the general metabolic activities of the body.

Thus, Mouriquand[7] has described two types of metabolic faults occurring at the menopause, both characterized by obesity, resulting from the disturbed function of the sympathetic nervous system. He describes such symptoms as diabetes, gout, biliary lithiasis, psoriasis, skin disorders, chronic rheumatism, renal and vascular diseases, and loss of tolerance for carbohydrates.

The abnormalities of the menopause are beyond all doubt directly consequent to disturbance of endocrine balance and readjustment in metabolism and function at this period. Much remains to be learned as to the precise changes taking place, but the fundamentals are well established and an endocrine interpretation permits, for the first time, a comprehensive conception of the disturbances of the menopause.

Treatment: There are few conditions which have proved as amenable to treatment as the abnormalities of the menopause. This is the more remarkable when we remember that before the development of organotherapy there was perhaps no condition more resistant to treatment. In recognition of the pluriglandular character of the endocrine disturbance as well as by the clinical experience, pluriglandular therapy is indicated. Ovarian substance should be used in the treatment in perhaps larger dosage than in any other condition. Of the value of ovarian substance Graves says:

> "The value of ovarian therapy is seen in the treatment of patients who are suffering from functional deficiency or absence of the ovarian internal secretion. The most conspicuous examples of this are those who experience the vasomotor disturbances of the natural or artificial menopause, the symptoms of which consist chiefly of hot flushes, vertigo, etc. By the administration of a properly prepared extract these symptoms are, with some exceptions, greatly benefited or made to disappear entirely."

Hormotone should be administered in a dosage of 1 or 2 tablets three times daily, supplemented by 1 capsule of Ovarian Comp., which may be increased if the indications demand.

STERILITY

Sterility is the term used to describe a condition in the female in which impregnation is impossible. Such a condition is a result of such a variety of causes that any elaborate discussion of the subject necessitates a consideration of a great number of the conditions of gynecological practice, as well as the biological conditions underlying absolute sterility. It is a curious fact that in the greater number of the cases in which conception does not take place sterility is attributed to the female rather than the male. There seems little doubt, in view of such investigations as have been made, that the cause should be sought for equally in the

male. It is probably preferable that both the husband and wife should undergo examination and that the post-coital examination proposed by Dr. Max Huhner of New York should be carried out.

Four general causes of sterility in the female may be considered: (1) absolute biologic sterility, (2) sterility arising prior to puberty as a result of endocrine defects and resulting hypoplasia of the genital organs, (3) sterility arising as a result of abnormal function of the ovary, the other genitalia being normal, and (4) sterility due to structural defects, infections, etc. Absolute biologic sterility is probably rare.

Supplementing these general classifications of sterility, it is well to consider that in cases in which conditions for fertilization are not ideal various apparently slight factors may determine impregnation. Reynolds and Macomber[8] describe such factors under the title of "Relative Fertility." They point out that such factors as diet, climate, racial and other characteristics influence the problem.

The treatment of cases due to structural defect, infection, etc., is surgical or local. In cases with an endocrine disturbance as the cause, organotherapy is valuable. Bandler has had very favorable results:[9]

> "I am now using extract of the whole ovary, thyroid and ovarian residue with an occasional dose of morphine for threatened miscarriage and the same preparation without morphine for repeated miscarriage, no longer paying exclusive attention to the Wassermann side of the question. The results are so excellent in both these conditions that I consider them the best test and the best proofs of endocrine therapy in the whole realm of gynecology.
>
> "It is only a slight step from this experience to the conclusion that, if these gland extracts aid in preserving the contact of the ovum and its continued growth, they must of necessity have the same power in promoting embedding of many a fecundated ovum which, without this aid, is cast off at menstruation. If these considerations concerning ovary, tube and decidua be true, the way to treat these conditions is clearly pointed out to us. We must substitute those internal secretions which are lacking or we must excite the action of certain of those internal secretions in order to cause the rupture of a Graafian follicle containing a ripe ovum; to give power to the Graafian follicle to secrete an enzyme which will enable it to rupture; to stimulate the lining of the tubes so that the cilia will function and to exert a trophic action on the endometrium which will permit the embedding and retention of a fecundated ovum. In other words, we stimulate by extracts of the glands which normally preside over those functions. On the other hand if the action of the ovaries and associated supporting glands be increased and the patient menstruates too often or too profusely, . . . then we are dealing with endocrines unusually assertive or a uterus too greatly stimulated. Here we must inhibit these stimuli and diminish menstrual function by endocrines or by resection of part of each ovary.

"Although the usual treatment of sterility as I now practice it consists mainly of two preparations of ovarian extract and one of thyroid, let me make mention of a few general considerations. We prescribe according to the patient's local signs, menstrual symptoms and constitutional makeup. We judge from a patient's appearance, her weight, the distribution of hair, character of the skin, cold, clammy hands, premenstrual phenomena, rate of the pulse, blood pressure, as well as of our local findings. Now the glands which stimulate genital function are ovarian secretion itself, thyroid secretion, suprarenal extract, pituitary gland posterior, in some cases probably anterior. The glands which serve to diminish the menstrual function are thymus and mammary, placental extract and in some phases probably thyroid.

"When a patient shows signs of myxedema or myxedema of the endometrium is suspected, thyroid is indicated. If patients show signs of hyperthyroidism or exophthalmic goitre, thyroid is not indicated. Patients having a typical dystrophia adiposo genitalis are the victims of a pluriglandular condition. To such patients we give pituitary extract in addition to ovary and thyroid. Patients with low blood pressure and asthenia suggest the administration of suprarenal extract and pituitary extract. Patients with large uteri and excessive menstruation, patients with large ovaries and excessive menstruation, whether these ovaries appear cystic or not, the so called oyster ovary, suggest the administration of thymus or mammary extract or placental extract or all three."

Bandler reports that out of a series of fifty consecutive cases, twelve patients in which the condition was not due to structural causes have responded to endocrine therapy and eleven became pregnant within three months after administering the gland extracts and one after administration for four months.

Solomon[10] reports that administration of glandular extracts, especially ovary, is useful in appropriate cases.

Treatment: In such cases Hormotone should be given in a dosage of 1 tablet three times daily and may be supplemented with one 5-grain tablet of ovarian substance three times daily or with one tablet of Ovarian Comp. three times daily.

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PART III

CHAPTER II

DIABETES MELLITUS

Diabetes mellitus is a disease of metabolism sufficiently common and grave in prognosis to command the attention of and stimulate to elaborate research many of the ablest members of the medical profession. It has been estimated (Joslin) that in the United States there are at least half a million diabetics and an inspection of the statistics compiled for foreign countries and cities shows diabetes to be an important item in the mortality statistics all over the world.

For the United States Joslin gives the following figures:[1] The deaths from diabetes in the registration area of the United States reached the maximum of 17½ per 100,000 in 1915. For the next five years they decreased as follows: 1916, 17.1; 1917, 17; 1918, 15.9; 1919, 14.9; 1920, 16.1. The figures for Boston show a parallel course. The maximum figure is that for 1915, 26.1 per 100,000. For the years following, the figures are: 1916, 25.2; 1917, 19.1; 1918, 17; 1919, 22.9; 1920, 23.2. The figures for New York City for the five year period ending 1919 are 19.8 per 100,000.

Joslin's statistics offer much encouragement in view of often repeated statements that diabetes is rapidly increasing along with other "degenerative diseases"— cardiac disease, arteriosclerosis, etc. Joslin believes that the decrease in mortality cannot be accounted for by lessening frequency of diabetes and that the improvement in modern treatment must be credited with a share in the general result.

Not only has the death rate decreased but, in addition, a remarkable extension of the duration of life in the diabetic has taken place. The average duration of life in cases of fatal diabetes in the city of Boston between 1895 and 1913 was 3.3 years. During 1915 it was 4.3 years and in 1920 it was 5.3 years.[2] The prognosis in diabetes mellitus is, therefore, better today than ever before and the accidents of diabetes — acidosis, coma, gangrene, etc.,— with careful attention to the details of treatment, are now very largely preventable.

Diabetes mellitus, as considered here and as encountered in everyday practice, is a disease of the pancreas (at least the pancreas is the central factor in the condition) resulting in deficient internal secretion and general inability to utilize glucose. The pancreatic disturbance may be either anatomic or functional, the exact pathology still remaining indefinite, but the fundamental characteristic of all true diabetes is definite lessening of the ability of the organism to metabolize sugar. The patient presents symptoms of progressive loss of weight, thirst, asthenia and hunger. Glycosuria, or the presence of sugar in the urine in abnormal amounts, is a constant finding and remains today a crucial point in diagnosis and in determining treatment. It may be mentioned that sugar is normally present in the urine in very small quantities. The quantity is not sufficient, however, to give a positive reaction to the

ordinary clinical tests, but it has been shown by Prof. S. R. Benedict, using a special technique for removing some substances which interfere with the reaction, that normal urine contains a small quantity of sugar, about one half of which is glucose.

Etiology

The Pancreas as the Central Factor in Diabetes

The nature of the factor giving rise to disease of the islands of Langerhans, or to functional disturbance of the production of the internal secretion from this tissue, is unknown. Many facts attendant upon the establishment of diabetes are known, however, and these, taken with a progressively enlarging knowledge of the mechanism of diabetes, have largely and favorably influenced the treatment and measures of prophylaxis. Early clinical observations and animal experiments had suggested a relation between the pancreas and diabetes, and an internal secretory function having some relationship to the carbohydrate metabolism was more or less clearly recognized by a number of observers before the researches of von Mering and Minkowski in 1889 established the relation between pancreatic function and experimental diabetes. These observers found that complete removal of the pancreas was invariably followed by diabetes and a glycosuria which remained constant. This glycosuria persisted irrespective of the food intake, and the other symptoms characteristic of diabetes were observed in the animals. They found, also, that the percentage of blood sugar increased, that acetone bodies were formed in the urine, that the liver lost its glycogen and became fatty, and that the condition was progressive and invariably fatal. If only a portion of the pancreas were removed, these changes did not take place. Subsequently, it was ascertained that an amount of pancreatic tissue as little as one-fifth to one-fourth of the organ was sufficient to protect the animal from diabetes. When these results were confirmed by other observers it was evident that a definite relationship had been described and the internal secretion of the pancreas, therefore, became an established fact based upon some of the most convincing experimental work in endocrinology. All opposition to the work of von Mering and Minkowski was successfully met, so that today the predominance of opinion remains that the pancreas is the central organ concerned in carbohydrate metabolism and that diabetes is a result of a break-down of its function in the utilization of sugar. Allen's statements as to this point are quite clear: "Clinical diabetes arises regularly on the basis of pancreatitis," and again, "It is now sufficiently established that the normal cause of diabetes is pancreatitis."

Disease of the pancreas may result from acute or chronic infection, or functional insufficiency may arise without known cause. Interference with the circulation or drainage from the ducts, obstruction due to gall stones, focal infection of the teeth or tonsils, syphilis or pus pockets in any site, may be found to be causative. The sexes seem to be about equally affected and diabetes occurs at every age of life. Heredity appears to be a factor and some races seem to be predisposed (Jews and Hindus).

Obesity and Overnutrition Predisposing Factors

The relation of obesity and overnutrition to diabetes is one of the most important and practical from the standpoint of prophylaxis and treatment that has yet been observed. In 75% of a series of 1,000 of Joslin's cases, there was a definite history of preceding obesity. Between the ages of 31 and 40, only 12% of his cases who developed diabetes were under-weight, and after 40 years of age but 6% or less. In another series of cases he found a history of excessive indulgence in food in two-thirds of the number of cases. The observations of others fully confirm the remarkable association of diabetes with obesity and overfeeding, which justifies the statement of Joslin, "All other considerations in the etiology of diabetes drop out of account when the possibility is recognized of preventing the disease by simply maintaining a normal weight."[2]

Among theories of causation that of primary origin in the nervous system may be mentioned. Naunyn held that disturbances of the nervous system were equally important as disease of the pancreas in causing diabetes and the literature has always shown a percentage of authors who believed in a nervous origin. The "*sucre piqûre*" of Claude Bernard has seemed to those holding this view to offer some experimental confirmation (see page 192). Of recent years there has been a noticeable tendency to consider diabetes as a somewhat more complex condition than the advocates of the simple pancreatogenic theory admit. In most of these the important part of the pancreas in diabetes is recognized but the part of the other factors is emphasized. Cammidge, in *The Practitioner* for June, 1922, recognizes several types (pancreatic, hepatic, concurrent) of diabetes, some originating in organs other than the pancreas. These have been largely established upon the basis of the "difference-value" of the sugar and total carbohydrates in the blood.

> "Having established by animal experiments and observations on cases of pancreatitis in the human subject that a relation of this description between the blood-sugar and difference-value curves is characteristic of disturbance of the functions of the pancreas, it seemed likely that by the same method it might be possible to ascertain whether diabetes was, or was not, invariably due to disease of the pancreas. As it happened, several of the earlier cases gave typical pancreatic, or opposed, curves, but as the investigation progressed it became evident that this type of curve was by no means constant and two others were subsequently differentiated. . . . Although the number of cases so far investigated is too small to allow of reliable conclusions being drawn as to the relative frequency of the various types, there is, I think, sufficient evidence to make it highly probable that clinical diabetes is not a single simple pathological entity, but a symptom complex, which may develop along at least three lines, of which disturbances in the functions of the pancreas is one."

Falta recognizes diabetes with gross lesions of the pancreas, particularly the islet tissue, in which this defect is alone sufficient to explain the condition. This he calls "pancreatogenic" diabetes. There are,

however, more frequently encountered types in which nervous manifestations are characteristic. He describes two such types, differing in the character of the nervous symptoms. In the first type, the psychic and nervous symptoms predominate and may characterize the condition for years. In this type, Falta suggests that it might be possible to demonstrate a constant hyperexcitability of a certain part of the sympathetic system, as a glycosuria of the adrenal type seems to always be present, attended by the other signs of adrenal action (vascular and cardiac signs). The second nervous type is characterized by the predominance of the alimentary factor. The psychic factor is not in evidence and there are no manifestations of sympathetic hyperexcitability until late in the course of the disease. In the later stages of both types there is evident the psychic and nervous element.

Falta suggests that there may be a congenital weakness of the embryonic groundwork (*anlage*) of the islet tissue, which makes the adult islands more susceptible to injury — infection, intoxication, etc. — and this would explain the rapidly progressive grave diabetes in young children. In the usual type of diabetes the pancreas is probably only relatively weak as compared to the activity of the chromaffin tissue, due to a strong excitation of the nervous centers regulating this tissue. When the pancreas is entirely normal the balance between the pancreas and adrenal action is maintained. In the nervous types of diabetes, the hyperexcitability arises *primarily*, and in the pure pancreatogenic form it occurs *secondarily*. The causes of the abnormal excitation of the nervous system are unknown.

Falta does not regard experimental diabetes and clinical diabetes as identical and, therefore, looks further than the pancreas for an explanation of the cause. He says:

> "In experimental pancreatic diabetes only the pancreas is absent, all the rest of the manifestations are secondary; in general human diabetes there exists, however, a disease of the whole apparatus regulating sugar metabolism (nervous centers in the medulla and brain stem, connecting paths, pancreas and chromaffin tissue), with insufficiency but not complete absence of one part and more or less independent hyperexcitability in the other parts."

Langdon Brown[3] regards diabetes as a clinical complex, the result of increased metabolism, a mechanism acting largely through the sympathetic and the endocrine glands. He stresses the importance of the sympathetic and the parasympathetic in the vegetative processes and in mobilization of blood sugar. Diabetes is a result of disturbance of this sympathetic-parasympathetic-endocrine system, in which the mobilization of carbohydrates is but one phase. The importance he assigns to these elements is expressed in the following:

> "Diabetes is, then, a sign of exaggerated metabolism, evoked through the sympathetic and the associated endocrine glands, which first asserts itself in relation to the most abundant food material, but as it advances expresses itself in relation to all."

The question of the identity of experimental and clinical diabetes is important. If it can be shown that they are identical, many factors

ternal secretion of the islands of Langerhans exerts an inhibitory influence on carbohydrate metabolism, which in general is opposed to the secretion of the adrenal medulla. It may perhaps equally be held that it has a specific selective action on the glucose molecule in preparing it for combustion by the cells and in making its oxidation by the cells possible. That it has both functions is not improbable.

Carbohydrate Metabolism

As the outstanding characteristic of diabetes, irrespective of all theories of causation, is decreased capacity for the utilization of carbohydrates, some of the chief facts of carbohydrate metabolism may be briefly presented, preliminary to a discussion of diabetes pathology. The carbohydrates are the great energy producers of the animal organism and normally, by reason of their ease of combustion, meet the greater part of the energy requirements of the body. The carbohydrates of the food are absorbed into the blood as monosaccharids, principally as dextrose (glucose) and perhaps, also, in some small amount, as levulose and galactose. These sugars form one (and the most important) source of the glycogen which is stored in the liver and large muscles (about 50% in each) and liberated again as dextrose for physiological oxidation in amounts requisite for the changing needs of the organism. In addition to the carbohydrates, protein foods in the process of splitting into the simpler amino bodies also give rise to glycogen, and the glycerol resulting from the splitting of fats is converted into glucose. It is probable that all the carbohydrates, regardless of their source, endogenous or exogenous, and irrespective of their character, are first converted in the process of assimilation to dextrose and are then converted into glycogen for storage and reconverted into dextrose for the physiological oxidations. Even the closely related monosaccharids such as levulose are first transformed into glycogen and then to dextrose, for it is apparently only dextrose that is available in any appreciable extent for these oxidations in the tissue cells. It is well known that diabetics may continue to excrete glucose long after the withdrawal of carbohydrates and such amino acids (protein "building stones") as glycin, alanin, aspartic and glutanaminic acids have definitely increased glucose excretion in the urine. In fasting diabetics, when all food is withdrawn, the tissues are drawn upon and by the resulting catabolistic process the body protein, glycogen and fat yield glucose which continues to be excreted in the urine, just as glucose from exogenous sources. This amounts to from 50 to 100 grams per day in the case of an individual of ordinary body weight.

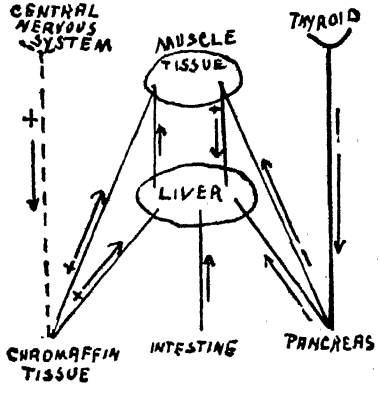
The liver is a temporary storehouse for the storage of sugar absorbed in quantities from the intestine and provides a means for the regulated release of dextrose and the maintenance of a balance for the organism's needs. Glycogen is transformed into dextrose through the agency of the powerful diastatic enzyme, glycogenase, which is found in the liver, blood and lymph. The mechanism of the action of glycogenase has never been clear but it is very important, as an explanation of its action would explain, perhaps, hyperglycemia, glycosuria and in large measure

the diabetic process. Most theories have largely assumed some inhibition of the action of glycogenase in the liver which as a balanced reaction may result in the release of sugar as this balance is disturbed. As sugar is consumed in the body, more glycogen is converted into sugar and normally the blood sugar content remains constant within narrow limits (between 0.1 to 0.2 per cent.). The regulation of this liver action may be through nervous pathways or, as is now the prevailing opinion, through hormone control. In either case, the effect probably is that of removing or lessening the inhibitory agent to glycogenase or a setting free of glycogen from some liver cell combination, so that the glycogenase is free to act upon it.

Endocrine Glands Associated with Pancreas in Sugar Metabolism

Since the experiments of von Mering and Minkowski, the pancreas is universally recognized as the central factor in carbohydrate metabolism. The explanation of the method by which this influence is exerted and the part of the other endocrine glands, principally the adrenals, thyroid and pituitary, remains for the future. The influence of the thyroid is undoubted and in hyperfunction tends to lower carbohydrate tolerance and produce hyperglycemia and glycosuria after the ingestion of smaller amounts of sugar than usual — after 100 grams of glucose. Hypothyroidism, on the other hand, results in raising tolerance. The pituitary has an action resembling that of thyroid in lowering carbohydrate tolerance in states of excessive function. The adrenal glands also exert an important action in mobilizing sugar, and glycosuria may result through their stimulation or after injections of adrenalin. The action of all these appears to be of opposite kind to that of the pancreas and may be affected through their known action on the vegetative nervous system.

The following diagram, a modification by Falta of von Noorden's scheme, is helpful in understanding what is known of their relations (except the hypophysis).



The line from the intestine relates to the impetus received from the intestine to the liver for the storage of sugar (from absorbed food).

" 'The line of dashes represents nerve paths; the solid lines represent blood paths. The arrows show the direction of the excitation; the sign + or − behind them means whether the stimulus transmitted by the respective path increases or diminishes the specific activity of the organ in question,' whether it acts assimilatorily or dissimilatorily."[4]

Effects through Vegetative Nervous System and Adrenals

The sugar puncture (*piqûre*) of Claude Bernard, a puncture of the medulla between the 10th cranial and auditory nerves resulting in a glycosuria, was followed by much research, and the subsequent observation that stimulation of the great splanchnic nerve gave similar results led to the conclusion that there was a "sugar regulating center" in the medulla; the fibers of the splanchnic originating there and passing to the liver regulate the rate at which glycogen is transformed into dextrose in the liver. Another view, also assuming a nervous control in some part, involves the adrenals. This view holds that the adrenals are stimulated reflexly through the vegetative (great splanchnic nerve) nervous system and that epinephrin thus thrown into the circulation acts on the liver cells, causing a conversion of glycogen to sugar (overcoming a theoretical inhibitory action of the internal secretion of the pancreas). Support for this theory is found in the fact that after ablation of the adrenals neither *piqûre* nor splanchnic stimulation gives rise to glycosuria and that the action of epinephrin pharmacologically undoubtedly causes glycosuria. Moreover, such a mechanism would go far to explain the glycosuria arising during emotional states and nervous conditions. The facts in favor of a nervous or a nervous-endocrine mechanism in the regulation of sugar combustion are here presented, as it appears that in some degree they are constant factors in the process, but that they are minor and of less importance than the endocrine (pancreatic hormone) there seems no doubt. The pancreatic hormone, the thyroid, pituitary and adrenal hormones, and the vegetative nervous system appear to form a system for the control of carbohydrate metabolism that is as yet not well understood.

Pathology of Diabetes

The normal individual has a high capacity for the metabolism of carbohydrates and excessive quantities are ordinarily oxidized without developing glycosuria. The amount which can be assimilated without leakage into the urine is the "assimilation limit" and ranges from 200 to 300 grams of glucose. The glucose tolerance test used in the diagnosis of early diabetes assumes a diabetes or a potential diabetes if glycosuria develops after the ingestion of 100 grams of glucose. Various methods for determining the actual capacity of the organism for the utilization of glucose have been used. Oral administration involves errors due to varying degrees of absorption and digestive disturbances themselves, as well as the sudden unloading of an amount of glucose into the circulation which is far beyond that with which the organism normally has to deal.

Rate of Combustion of Sugar in the Body

Woodyatt, Sansum and Wilder devised a method which has contributed more to our understanding of these limits than all others. These observers conceive the capacity for sugar utilization to be dependent upon the rate at which the cells are able to function in using up the sugar supplied to them. Therefore, to describe the functional ability in utilizing sugar, it is necessary to state both the total quantity of sugar and the weight per unit of time in which it is supplied. Their

procedure involved the use of a pump for the continuous control of the intravenous injection of sugar, by which means it was possible to determine the limits of the ability of the organism to burn sugar thus introduced. They found that if the sugar is supplied at the rate of .8 to .9 grams per kilogram of body weight per hour, it is burned by the organism and without any loss into the urine. When .9 to 2 grams per hour are supplied, glycosuria appears, and above 2 grams per hour a larger percentage of the glucose in excess of this amount is excreted in the urine.

It is characteristic of diabetes that the liver rapidly loses its glycogen store and carbohydrate feeding is useless in preventing this. The percentage of blood sugar rises and glycosuria develops (ordinarily, glycosuria develops when the blood sugar concentration reaches .17 gm. per cent.). The explanation of hyperglycemia and glycosuria will, therefore, largely extend our knowledge of diabetes, even though we agree with Abderhalden:

> "Up to the present, the most pronounced symptom, that of glycosuria, has dominated the entire investigation of problems concerning diabetes, and it is very probable that this is the reason why the disease is, as a whole, so little understood."

A fuller understanding of the glycosuric process, however, would materially aid us, even if it did not inform us as to the ultimate (nervous?) causes. Theories as to the cause include defects in the storage mechanism, abnormal production of sugar and inability of the tissue cells to utilize sugar, thereby permitting its accumulation in the blood, and the theory of increased renal permeability. It is evident that in the diabetic process most of the phenomena of diabetes would be susceptible of more or less complete explanation by any of these defects. It has been shown that increased rate of supply of glucose in normal animals within certain limits increases the capacity for utilization and that only when these limits have been exceeded does sugar leak into the urine. Until these limits have been reached, the increased utilization prevents escape into the urine, even though the amounts are excessive, but when these limits have been exceeded the sugar rapidly escapes and is eliminated almost quantitatively. In normal healthy animals this power of increased utilization makes any excessive alimentary glycosuria almost impossible, for increased supply is met by increased utilization.

Diabetes a Condition of Impaired Sugar Utilization

It becomes evident, therefore, that the failure of the cells to utilize the sugar in which they are bathed and which eventually reaches a high concentration is the fundamental reason for the hyperglycemia and the subsequent glycosuria. To account for a glycosuria from endogenous sources would be to assume that these increased utilization limits had been exceeded, with a consequent increased metabolic rate and a high respiratory quotient. It is well known that large numbers of cases of advanced diabetes, with heavy glycosuria, are characterized by normal or low respiratory quotient and no increase in the metabolic rate. That increased utilization does not take place is evidenced further by failure to obtain increased respiratory quotient by administration of glucose to diabetic animals. The diabetic process, therefore, is characterized fundamentally by an inability of the tissues to utilize glucose.

Starling and Knowlton endeavored to ascertain the rate of sugar combustion in the isolated heart of experimental animals and seemed to show that a normal heart, perfused with normal blood, consumes about 4 milligrams per hour for each gram of heart muscle, whereas the consumption of sugar in the heart of a diabetic dog was minimal or absent. Subsequent investigation of this data by Starling and Patterson revealed errors which make the conclusions unreliable, due to the fact that the heart preparations may either store away sugar as glycogen or may at the time of the experiment contain considerable glycogen, which may be burned without first using the sugar of the perfusion fluid.

Nature and Source of the Pancreatic Hormone

The immediate cause of the faulty utilization is the disease (functional or anatomic) of the islands of Langerhans of the pancreas. The islands were suggested as the seat of the internal secretion of the pancreas by Laguesse in 1893, and Opie has prominently sponsored the island origin of the antidiabetic internal secretion in this country. The precise part played by the pancreatic hormone is uncertain and may be either in regulating the conversion of glycogen to dextrose or in the catabolic processes whereby the sugar is consumed in the tissues. Some investigators hold the opinion that it has both these functions. While innumerable and conflicting hypotheses have appeared, our knowledge does not permit us to generalize further than the statement on page 189.

In diabetics there are found various pathologic states of the islands and in experimental animals the usual result following pancreatitis, artificially produced and accompanied by diabetes, is fibrosis and atrophy. Hydropic degeneration of the islands, also, is found in many cases of diabetes, although this is probably a result rather than a cause. There is no agreement among pathologists as to the significance or constancy of the several types of lesions described in the pancreas of diabetes. Diabetes has undoubtedly occurred in cases in which there was no demonstrable lesion in the pancreas. Whether these cases can be explained as functional deficiency without the development of structural defect and due to defects in the nervous control through the "sugar control center" or through defects of the associated glands cannot be answered positively.

Insuline

The efforts to extract from the pancreas the active substance (hormone) responsible for the utilization of glucose were first made shortly after the experiments of von Mering and Minkowski had demonstrated the relationship of the pancreas to sugar metabolism. Among these were those of Minkowski himself. The earlier results were unsuccessful, but within recent years reports of definitely successful experiments began to appear. Zuelzer, Scott, Kleiner and Meltzer, Kleiner and Murlin, and Kramer and Paulesco all prepared pancreatic extracts which gave evidence of antidiabetic properties, and on injection into animals reduced blood sugar.

Scott's Experiments

In 1911, Scott[5] reported the results of his experiments with pancreas extract in diabetic dogs. He took into account the theory which seems to have been first advocated by Leschke, that the enzymes may destroy the internal secre-

tion, but added another possibility and one which appears to be more tenable, namely, that the inert extracts previously described might be due to chemical changes — that is, oxidation. He said:

"Another point that seems not to have been sufficiently considered is the possibility that the internal secretion may be readily destroyed by oxidation during the preparation. This seems probable in the light of our experience with adrenalin." "It seemed worth while to see if the sugar output could be lowered by an extract in which precautions were taken to prevent (a) the effect of digestive enzymes on the internal secretions as well as on the subject, and (b) to prevent the oxidation of the internal secretion while being prepared from the gland." "It was hoped that the presence of the digestive enzymes could be eliminated by the atrophy of the gland which follows complete ligation of the ducts, but, after several attempts in this direction which proved futile so far as complete atrophy was concerned, this method was abandoned as impractical. In subsequent work these enzymes were rendered inactive at once by a high percentage of alcohol, and were later killed by long continued contact with strong alcohol. . . . Intravenous injection of the pancreas extract, prepared as above, into dogs rendered diabetic by complete pancreatectomy diminished temporarily the sugar excretion and lowered the D/N ratio in the urine."

Kleiner's Experiments

In 1919, Kleiner[6] supplemented the work of Kleiner and Meltzer[7] in 1915, in which they found that, whereas in diabetic animals intravenous injection of dextrose ordinarily kept the blood sugar level far above the normal, if pancreatic extracts were introduced with the sugar the animal handled the sugar in an approximately normal manner.

Kleiner used a fresh, faintly acid aqueous solution from dog's pancreas, unfiltered and without the addition of sodium carbonate. Since the chemical nature of the effective pancreas principle was unknown, complicated processes of purification were avoided. In Kleiner's experiments, although no attempts were made to prove actual combustion of sugar, there was no increase of glycosuria. On the contrary, there was a reduction, and the effects were not dilution phenomena and they were not due to the introduction of alkalies.

Experiments of Murlin and his Associates

Murlin,[8] who had carried on earlier an extensive research into the effects of alkali and pancreatic extracts on respiration after pancreatectomy, demonstrated in 1921 that perfusates of the pancreas with Locke's or Ringer's solution and with 0.2% sodium bicarbonate, or 0.5% glucose, raised the respiratory quotient in a depancreatized and diabetic animal.

Clark's Perfusion Experiments

Clark, in 1917, prepared a product containing the internal secretion of the pancreas in a different manner from the previously used extraction methods. He[9] found that the sugar of a solution perfused through the pancreas is not acted upon, but that the pancreas contributes something to such a solution that is indispensable for the utilization of the sugar by muscle cells.

"The experiments indicate that the pancreas when perfused aseptically with Locke's solution containing physiological concentration of dextrose does not alter the reducing properties of the perfused solution. The pancreas, however, seems to supply something to the Locke's solution circulating through its arteries, which in some way brings about a utilization of sugar by the living heart to an extent that does not occur with the heart alone. This pancreatic substance possesses some of the characteristics of an enzyme."

Clark found this perfusate had two effects, one, a removal of reducing sugar by a condensation process and a second, a removal of sugar by hydrolysis or oxidation. He says:

"The evidence suggests at least that the substance or substances obtained by perfusing the pancreas may be concerned in the normal activity of the pancreas upon sugar metabolism."

Paulesco's Work

Paulesco[10] found that there was a distinct reduction of sugar and other substances following the use of an extract of the whole pancreas made by extracting the whole pancreas with a sterile 0.7% sodium chloride solution.

Banting's Work

In 1922, Banting[11] at the University of Toronto, with the assistance of Best, using a method previously attempted by Scott, prepared a pancreatic extract which gave the following results in diabetes:

1. Blood sugar was markedly reduced, even to the normal value.
2. Glycosuria was abolished.
3. Acetone bodies were made to disappear from the urine.
4. The respiratory quotient gave evidence of increased utilization of carbohydrates.
5. Definite improvement was observed in the general condition of these patients, and in addition the patients themselves reported a subjective sense of well being and increased vigor for a period following the administration of the preparation.

The conception had arisen that the trypsin in pancreas substance destroyed the internal secretion during preparation, if special measures were not taken to eliminate it. Following the plan suggested by Scott, Banting and Best ligated the pancreatic duct of animals and after a few weeks removed the pancreas in which the enzyme producing cells were found to be degenerated, leaving the insular part containing the internal secretion unaffected. Extracts of this tissue gave the characteristic effects in reducing blood sugar. Subsequently a method of preparation from whole adult pancreas and a method of standardization were developed.

Insuline, which was so named by Schäfer in 1916, became a therapeutic possibility in 1922 as a result of the work of Banting and Best and of MacLeod, who later collaborated. It represents the active principle (hormone) of the pancreas which is concerned in carbohydrate metabolism. The fate of the sugar following insuline injection is not well understood. Some evidence shows a greater consumption of sugar, and at least it is removed from the blood.

Hepburn and Latchford[12] found that:

"The average sugar consumption of the isolated rabbit heart perfused with Locke's solution was found to be 0.87 mgm. per gram per hour. When insulin of proved potency, as tested by its ability to lower the blood sugar in normal rabbits, was added to the perfusion fluid, the average sugar consumption rose to 3.06 mgm. per gram per hour."

They show that pancreatic extract increases in marked degree the capacity of the muscle of the isolated heart to remove the sugar of a perfusion fluid. They found no evidence that the reducing sugar had been converted into a non-reducing sugar. At Toronto a research to determine whether pancreatic extract exerts a fundamental action on the control of blood sugar and is active in normal as well as diabetic animals has shown that alcoholic pancreatic extract, when injected subcutaneously into normal rabbits, causes a fall in the percentage of blood sugar, and, making use of this observation, there has been established a physiological assay for pancreas extracts.

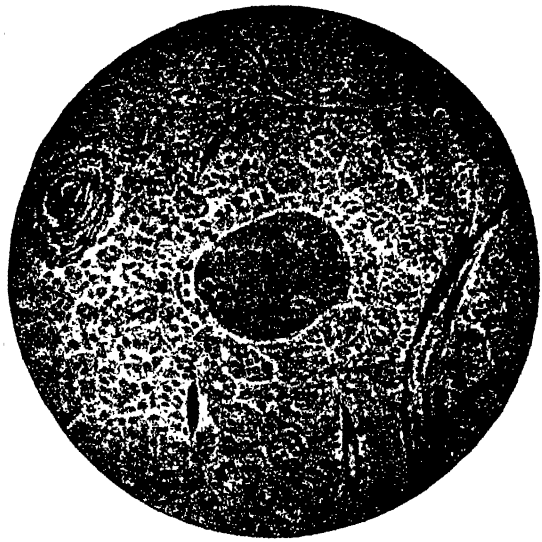
It becomes clearer from work already done that the pancreas is important in sugar metabolism, by reason of its internal secretion and not through an immediate effect on sugar of the blood passing through it. The pancreas very probably contributes an internal secretion that acts directly in the individual cell in utilizing sugar, and the effect is a fundamental one taking place in normal physiology.

For the place insuline has in diabetic treatment, see page 210.

Summary: Reviewing briefly some of the data discussed in relation to diabetes etiology and pathology we may summarize: Diabetes mellitus is a disease characterized fundamentally by decreased capacity of the organism for the utilization of glucose. The immediate cause of this defect is functional or anatomic disease of the islands of Langerhans of the pancreas, resulting in deficiency of its internal secretion. The more remote, or primary, causes may be in the associated endocrine glands — pituitary, thyroid apparatus or adrenals — and the vegetative nervous system with which the functional activity of these glands is intimately related. Nervous and emotional disturbances, resulting in glycosuria, act through this endocrine-vegetative system. The mode of action of the pancreatic hormone is unknown, but there is evidence that it acts both in exerting an inhibitory influence on glycogenolysis or release of sugar from the liver, and in preparing for, or in some manner aiding in, the utilization of the dextrose molecule by the tissues.

Acidosis or Ketosis

One of the danger points in the treatment of diabetes is the development of acidosis, always a grave complication and one which all treatment attempts to prevent. Acidosis is a general term descriptive of a disturbed relation between the acid and basic elements of the blood, in which the H^+ion concentration is increased relatively at the expense of the basic elements. The remarkably constant reaction of the blood is maintained by the peculiar reaction of the "buffer salts", principally NaH_2PO_4 and $NaHCO_3$, acid sodium phosphate and sodium bicarbonate.



Section from normal human pancreas, showing normal island of Langerhans.

Section from pancreas of diabetic subject. Island of Langerhans surrounded by sclerotic capsule and showing sclerotic and degenerative changes.

Specimens prepared especially for this work.

No description of the chemical equilibria entering into these reactions can be given here, but it should be noted that the sodium bicarbonate in the blood is of fundamental importance in maintaining the H^+ion concentration requisite for health through the equilibrium H_2CO_3: $NaHCO_3$, in which the H^+ion concentration is constant. So long as the $NaHCO_3$, the "alkaline reserve," is present in sufficient concentration, the addition of acids does not serve to raise the acidity. Acidosis occurs in many conditions as a result of the accumulation of various acid substances and of depletion of the basic elements. The acidosis of diabetes, however, is but a special form of acidosis. The disturbed acid-base equilibrium is here due to the addition of two acids to the body fluids, beta-oxybutyric and aceto-acetic (acetone bodies), acetone and aceto-acetic having a ketone group, hence the name sometimes given to the condition — ketosis.

The presence of these acids, therefore, is the condition with which the physician has to deal in the acidosis developing during the course of diabetes. These acids are formed as a result of imperfect combustion of fat, for the complete combustion of which an adequate quantity of carbohydrates must be burned at the same time. The proteins also give rise to substances, which it has been shown are converted into substantial quantities of these acids. Apparently the easily oxidized carbohydrates are necessary to complete oxidation of the fats — the oxidation of the two substances proceeding at the same time. In the failure of sugar combustion characteristic of diabetes, therefore, the intermediate products of imperfect fat oxidation accumulate and acidosis of a very grave kind develops. In imperfect fat combustion, the oxidation of the fatty acid ends when the 4-carbon butyric acid is formed — CH_3 CH_2 CH_2 COOH, no further oxidizing off of carbon atoms taking place. Further oxidation results in beta-oxybutyric acid, CH_3, $CHOHCH_2$ COOH, and aceto-acetic acid, CH_3, $COCH_2$ COOH, and acetone, CH_3 $COCH_3$ (the latter probably unimportant).

Not only are the carbohydrates themselves effective in preventing the formation of these substances but protein as well, though in much less degree. Those compounds which give rise to aceto-acetic acid are called ketogenic substances. Those which are converted into dextrose are antiketogenic.

Hubbard and Wright, as a result of their studies on acetonuria, reached the following conclusions:[13]

> "(1) That the mechanism which controls the formation of increased amounts of the acetone bodies can be regarded as a molecular reaction or balance between ketogenic substances such as the fatty acids and antiketogenic substances such as glucose; (2) that protein figures as an antiketogenic compound only to the extent of the glucose which it can yield in the organism; (3) that glycerol, when fed as a part of the fat molecule, figures as an antiketogenic compound only to the extent to which it forms glucose in the organism; and (4) probably that glycerol so fed does figure as an antiketogenic compound to the extent to which glycerol itself can yield glucose."

Their work and that of Shaffer is based upon the thesis that the intermediary product, aceto-acetic acid, is burned with difficulty but that on combination with dextrose, or one of the degradation products of dextrose, a compound results which is readily consumed.

The importance of these principles to the diet of the diabetic is at once apparent, as it becomes imperative to allow sufficient carbohydrates (antiketogenic substances) in the food to carry on the combustion of fats beyond the acid-forming stages. It is to be remembered, also, that protein is of much less value for this purpose than the carbohydrates themselves. Woodyatt says:[14]

> "There is, for any given individual at any given time, a definite ratio between the quantity of glucose oxidizing in the body and the maximum quantity of ketogenic fatty acids that can be oxidized in the same time without the appearance of abnormal amounts of the acetone bodies. In other words, the quantity of oxidizing glucose fixes an upper limit to the quantity of ketogenic fatty acid that can be completely oxidized at the same time."

Carbohydrates should be given in the full amounts permitted by the degree of tolerance in the individual case, so that the urine shows no leakage. Acidosis under such treatment is not likely to result.

> "It follows from the foregoing that the rationale of dietetic management in diabetes is to bring the quantity of glucose entering the metabolism from all sources below the quantity that can be utilized without abnormal waste; and to adjust the supply of fatty acids in relationship to the quantity of glucose, so that in the mixture of food stuffs oxidizing in the body the ratio of the ketogenic fatty acids to glucose shall not exceed limits compatible with freedom from ketonuria. When, as, and if, under these conditions of relative rest for the pancreas, the glucose using function improves, then the food supply may be increased gradually in so far as this can be done without disturbing the above relations."[14]

The regulation and maintenance of the proper ratio between these two classes of substance has been called the "ketogenic-antiketogenic balance." Various calculations have been made to determine the numerical value of this ratio, which range from 4 gm. fat to 1 gm. carbohydrate, to 1 to 1½ gm. fat to 1 of carbohydrate. These refer to the amounts of each which insure complete oxidation of the fat. Woodyatt says: "It would seem that for clinical purposes one will make no gross error if it is assumed that the ratio of higher fatty acids to glucose, which if exceeded will lead to acidosis, is likely to be close to 1.5 to 1 (in grams). This refers to the materials actually catabolized and to the diet only under stated conditions."

TREATMENT

As diabetes is a condition in which the fundamental defect lies in failure to utilize one of the principal foodstuffs — glucose — an intermediary product not only of carbohydrate but of protein and fat

as well, it becomes evident why the diet has always demanded so much attention in treatment. The diabetic organism is apparently able to use a certain quantity of glucose as well as the non-diabetic, but when the lowered limits of utilization have been exceeded the percentage of blood sugar rises and, having exceeded a certain value, is excreted in the urine. The diabetic diet, then, must be so adjusted that the quantity of glucose is brought within the limits of utilization, sufficient energy is produced, acidosis avoided, and the nitrogen equilibrium maintained. The ratio of foodstuffs in the diabetic diet varies greatly from the diet of healthy individuals. In health, more than half the calories are derived from the easily burned carbohydrates, whereas, with the lowered capacity for glucose in the diabetic, the caloric loss from this source must be made up from the other classes of foods, principally the fats (with their nine calories per gram as against four calories of protein).

The education of the patient is important and should include as much information on the practical subject of diet and cookery as is possible, as well as instructions in the methods of making a simple test for glucose in the urine. The patient must also realize that, with the reduction of his energy-producing powers, a readjustment in his habits of life is necessary and that a less vigorous, less active life is of the utmost importance.

Untreated diabetes becomes progressively worse, whereas with proper treatment, even in high grade diabetes, it is usually possible to prolong life and permit of a fairly normal existence with comparative freedom from the disturbing subjective symptoms. In milder diabetes, the results are vastly better and not only is the diabetes not progressive but definite improvement in the direction of a return to normal may be accomplished. Exercise within the limits of the patient's capacity is desirable. A systematic and limited use of the muscles of the body apparently aids metabolism and contributes to the general well-being. The large muscles, storehouses of glycogen, are given work which uses up glycogen, reduces blood sugar, and may increase in some degree the sugar tolerance. This is particularly important for the obese diabetic. Advanced diabetes is not so well treated by exercise, but for the maintenance of general health some regulated exercise is necessary in all but the most urgent cases. Exercise, however, should always be regulated so that the strength of the patient is not overtaxed and should be increased gradually, the guide being the subjective and objective symptoms in the patient. The cultivation of a tranquil, placid state of mind and mental repose is important and the relation of the psychic condition and the nervous system to diabetes has been described (see page 192).

Indirect Therapy

Dietetic Treatment

Despite the extensive research which has been carried on all over the world, there is no accepted and generally used system of dietetic treatment. Numerous empirical systems have appeared and have proved of value in many cases in which they have been used (milk, potato, oatmeal, rice cures), but a rational system, applicable to all classes of diabetes and subject

to calculated control to meet various conditions and with the various foodstuffs, has yet to become universally accepted and adopted. The regulation of the diet by the system and with the formulæ devised by Woodyatt appears to meet such requirements and will be described. Before this, however, the older and more conventional, yet very efficient, methods for diet control will be discussed.

The basic, underlying principle of dietetic diabetic treatment is that of undernutrition, which requires that in addition to restriction of certain kinds of food (carbohydrate) the total quantity shall be reduced. This principle will remain an enduring tribute to the American investigator, Frederick M. Allen, and stands as the most substantial contribution to the modern dietetic treatment of diabetes. It seems probable that the success of the various empirical systems of treatment which have been found of value may have been largely due to their conformity to this principle.

Modern research on diabetes diets takes into account the endogenous sources of food and the character of the metabolism and nutrition of the body during fasting. The dangers of the old high protein diet are generally recognized. Protein yields not only a large percentage of glucose (58%), but it also yields a high percentage of acids capable of causing acidosis. The increased metabolism and heat production of diabetes are also due to the stimulation of the protein — the "specific dynamic action" of Rubner. The increased nitrogen content of the urine observed under the older methods of treatment was due "to the large nitrogen content of the diabetic's diet, either because of his own tendency to replace with protein the carbohydrate calories lost in the urine or because of the very high protein content of the contemporary diabetic diet."[15]

It has been observed that the urine of some diabetics cannot be made sugar-free by fasting and this appears to be the case in lean diabetics or in those in which for some reason body fat is not burned, who metabolize their body protein with the consequent production of more glucose than can be burned and with leakage into the urine. It is evident, therefore, that it is the protein which must be limited — to quantities sufficient to maintain nitrogen equilibrium — and the carbohydrates given in quantities up to the limits of tolerance.

The diabetic diet is a restricted diet and should meet the caloric requirement of the patient, but not greatly exceed it. From 25 to 35 calories for each kilogram (2 1/5 lbs.) of body weight is perhaps sufficient for the majority of cases of diabetes. The undernutrition principle is devised to give rest to an active secreting tissue (islands of Langerhans), the progressive deterioration of which is conceived by Allen to be due to diets which make too great demands on its functional capacity, so that restriction of the carbohydrates (within the capacity for utilization) is of the first importance. The diet is first adjusted so as to make the urine sugar free. Various test diets have been arranged and may be used for the purpose. A diet composed of one gram of carbohydrate and one gram of protein for each kilogram (2 1/5 lbs.) of body weight will usually give a sugar-free urine and a normal blood sugar value within a few days. For the maintenance diet, the protein should amount to about one gram

or a gram and a half for each kilo of weight. The carbohydrates should be in amounts less than the limits of tolerance (determined by the appearance of sugar in the urine) and the fats should be kept moderately low. The additional food should be added gradually to the diet in daily additions of about 5 grams until the maintenance diet is reached — carbohydrates under the quantity sufficient to give glycosuria, protein in amounts to establish a protein balance, and fats in moderate quantities to give increased calories.

"Allen Treatment" Some of the measures included in the treatment usually referred to as the "Allen treatment" may be given as of proved practical value and forming good practice today. The patient is subjected to a preliminary fast (from one day to a week), during which the urine becomes sugar free. After an interval of 24 hours, during which no sugar has appeared in the urine, the first food is given. In some instances carbohydrates (as green vegetables), in increasing amounts of 10 grams daily up to the production of glycosuria, are given and if there is acidosis this is the best plan for relieving it. It may be preferable, however, to give a protein diet (meat, fish, white of eggs, etc.) with bran biscuit, vegetables (boiled in three waters to free from carbohydrates but leaving bulk), agar jelly, etc. The amount of protein varies with the severity of the case — in mild cases 60 grams and in very severe cases 10. In severe cases the protein may be low at first and then worked up to as much as 60 grams. This protein diet is usually given until the blood sugar decreases and there is some loss in body weight, although the patient loses less strength than on any other diet. Carbohydrate is given as the next article of food and may be given before the protein has been added in full quantity. During this time the nitrogen balance of the body is maintained at the level required to reduce the percentage of blood sugar to normal (from a number of days to months).

Maintenance Diet Carbohydrate is now added in as large quantities as possible, yet within the limits of utilization, so as to avoid a return of hyperglycemia. Fat may then be added and may require a reduction of the quantity of carbohydrates. The total protein of the maintenance diet is usually from 60 to 80 grams, or, in the case of children, as much as 2 grams per each kilogram of body weight. The requirements of calories is variable (depending on activity, weight of the patient, etc.) but in general from 25 to 35 calories per kilogram of body weight. Excess of calories is to be avoided, for hyperglycemia may result and compel reduction of the quantity or increased exercise.

Fasting Fasting undoubtedly affords rest to the pancreas with a lowered functional activity and a day's fast at regular intervals may be used as routine treatment. If not complete fasting, greatly reduced diet may be taken at intervals as part of the routine treatment. Food values may be calculated from tables and all foods should be carefully weighed. Calories are computed on the basis of 4 calories for each gram of carbohydrate and 4 for each gram of protein and 9 for each gram of fat. If at any time sugar appears in the urine, fasting may be resorted to until the urine is sugar-free.

The immunity of the diabetic to infection (pyogenic and many others) is markedly lessened and every patient should be instructed as to the danger of injuries and infections of the feet, fingers, etc. The dangers from this source are greatly lessened by maintaining a normal percentage of blood sugar.

Treatment of Acidosis

Immediate changes in the diet, withdrawal of fats, plenty of fluids, enemas and maintenance of the strength of the patient are demanded. Joslin describes his treatment as follows:

> "If, despite our efforts, acidosis threatens, the following routine treatment is recommended: (1) Reduce the total metabolism by placing the patient in bed and providing a nurse, to save all needless exertion; (2) Administer abundant liquids — 240 c.c. — each hour in order to promote the excretion of acid bodies; (3) Promote evacuation of the bowels not only to favor digestion but in order to enable, if desired, enemata of salt solution or water to be given in case water is not retained by the mouth; (4) Wash out the stomach in the first stages of treatment, because, frequently, coarse food is retained, which leads to vomiting, and loss of valuable hours; and (5) Administer moderate quantities of carbohydrate — either levulose, which is readily obtained in the form of orange juice, or, if this is disliked or for any reason contraindicated, oatmeal gruels and skimmed milk. I have avoided fat largely because it is more apt to upset the digestion of a patient upon the verge of coma, and second because from fat the acid bodies which lead to coma are formed. Recently, evidence has been submitted that body fat will be consumed if extraneous fat is not given, but at present it appears safe in the presence of threatening acidosis to cling to the above-mentioned plan of treatment, and if the body is to burn fat to let it select its own dose."

Alkalies may be used, although every effort should be made to clear up an acidosis by dietary means before resorting to this therapy, but its administration should not be delayed too long if it is evident that the condition is not under control. Sodium bicarbonate may be given and Allen states that when given by mouth it has never seemed dangerous and in some cases has appeared actually life-saving, in doses of from 40 to 100 grains daily. Bicarbonate may also be given by rectum (1 or 2 per cent. in physiological salt solution). Alkaline tablets (G. W .C. Co.) may be administered in a dosage of 2 tablets every hour during the day until an approximate degree of alkalization has been accomplished. For prevention of acidosis or administration at intervals in routine treatment this dosage may be greatly lowered. This tablet has a distinct advantage over sodium bicarbonate in that the quantity necessary for alkalization is distinctly less. Alkalies, however, need not be administered as a matter of routine treatment, but occasionally, if indications of acidosis appear, several days' treatment may prevent its development.

Diet Computation of Woodyatt

Woodyatt[14] has undertaken the problem of diet in diabetes from a different standpoint. He takes into account that the endogenous supply of glucose must be considered as well as the exogenous; that glucose is formed from fats and proteins as well as from carbohydrates; that the total quantity of glucose must be adjusted to the quantity of ketogenic acids formed. The endogenous sources of food are usually ignored in computing diets. The results of the experiments of numerous observers show that a normal man, weighing 50 kilograms, may produce 1,500 calories a day during a fast. He, therefore, catabolizes 75 grams of protein, 125 grams of fat and some carbohydrate from the stored glucose. Now, since it has been shown that "when there was much fat present little protein was consumed; when there was little fat much protein burned; and when there was no fat, protein alone yielded the energy of life" (Lusk), it is evident that fat in the diet may avoid the consumption of the tissue fat and prevent too large catabolism of tissue protein. The experiment quoted from Lusk is given of a dog "which in starvation burned 96 grams of fat. Voit gave 100 grams of fat with the result that it burned 97 grams. The fat ingested simply burned instead of the body fat, but the total amount of protein and fat burned remained the same." From these observations Woodyatt concludes that, if a diabetic produces from 1,250 to 1,500 calories by burning from 100 to 120 grams of his body fat during a fast, this quantity of fat taken in the food should leave the metabolism in the same state as before. In one case the fat would come from the body tissue and in the other from the food, but the quantity requiring internal secretions, enzymes and physiological work would be the same. "Fasting or placing on a fat-free, low carbohydrate diet to reduce glucose (in blood and urine) would not seem necessary or rational in the light of these facts." In fasting there is the danger that the body fat may be drawn upon to the extent that the subsequent body protein loss is so great as to weaken vital organs. Recognizing the difficulty of formulating diet instructions in terms of carbohydrate, protein and fat, and considering that these are not the substances which are finally used in the oxidations of the body but are reduced to simpler substances, — protein to amino acids and glucose; carbohydrates to glucose; fats to fatty acids, glycerol and glucose — Woodyatt constructed formulæ expressing these ideas which make possible the calculation of a diet in which the glucose presented for oxidation from all sources, endogenous and exogenous, is taken into account and a proper balance of fatty acids to glucose is maintained. Upon the basis of the observations (page 200), that if a ratio of 1.5 to 1 of fats to carbohydrates is not exceeded acidosis is unlikely to develop, the following formulæ have been constructed. The following tables give the percentage of intermediary products given by 100 grams each of fats, proteins and carbohydrates, and are used as a basis for these formulæ.

G = Glucose. FA = Higher Fatty Acid

100 gm. carbohydrate during metabolism yields 100 gm. G and 0 gm. FA
100 gm. protein during metabolism yields 58 gm. G and 46 gm. FA
100 gm. fat during metabolism yields 10 gm. G and 90 gm. FA

"If C=carbohydrate, P=protein, F=fat, G=glucose and FA=higher fatty acids (plus ketogenic amino-acids expressed in terms of higher fatty acid), we may say — as shown above — that the quantity of glucose which any given combination of foods may introduce into the metabolism is expressed by the equation: (1) $G=C+0.58+0.1\ F$ and that the quantity of higher fatty acid (and equivalents) may be expressed as (2) $FA=0.46\ P+0.9\ F$. When the ratio $\frac{FA}{G}$ exceeds a certain value, ketonuria develops. Assuming that this ratio is 1.5, then $\frac{C+0.58\ P+0.1\ F}{0.46\ P+0.9\ F}=1.5$, when the ratio of fatty acids to glucose is as high as it may be without ketonuria. Simplifying this we obtain $F=2C+0.54\ P$, or simply, (3) $F=2C+\frac{P}{2}$. If it is agreed that the ratio FA:G shall not exceed 1.5 and that the relationships expressed in equations 1 and 2 are given, then to estimate the optimal food combination or diet one may use equations 1 and 3. Given the quantity of glucose that the patient can utilize completely, assign this value to G in equation 1. Thus, if 100 gm. is the highest quantity of glucose derived from all sources that the patient can utilize, 100 gm. $=C+0.58\ P+0.1\ F$. In order to secure the maximal number of calories, the diet must clearly contain every possible gram of fat (at 9 calories per gram) that the value of G and the relations expressed in 1 and 3 will permit, and consequently the lowest possible carbohydrate protein fraction (at 4 calories per gram). Also, as between carbohydrate and protein, the protein must be as low as possible and the carbohydrate as high as possible, for 1 gm. carbohydrate yielding 1 gm. glucose and 4 calories provides for the normal oxidation of 1.5 gm. of higher fatty acid. On the other hand, 1 gm. protein having the same caloric value as carbohydrate yields less glucose to support fat combustion and besides this yields acetone itself. If the body weight of the patient be 50 kg. and 1 gm. protein per kg. is selected as a conservative minimum; then P becomes 50 gm. and $F=2C+\frac{P}{2}$ becomes $F=2C+25$. We have already made G=100 gm. Now, the glucose yielded by the 50 gm. protein will be 0.58×50, or 29 gm., leaving $100-29$, or 71 gm., to be distributed between carbohydrate and fat. In other words $C+0.1\ F=71$. From this we obtain $F=710-10C$. But we also have from the above, $F=2C+25$. So $2C+25=710-10C$, solving which C=57 gm. (57.08). Substituting this value for C in $F=2C+25$ we find F=139 gm. (139.16). Then, the optimal food combination that will fulfill the conditions and relations specified is: carbohydrate, 57 gm.; protein, 50 gm.; fat, 139 gm.=calories, 1,680."

In like manner, the percentages of the foodstuffs may be calculated for any diabetic diet, in which either the protein requirement or the glucose tolerance varies.

Showing Optimal Food Combinations When G=100 Gm. (In the Equation G=C+.58+.1 F); When FA : G=1.5; and When the Protein is 0, 25, 50, 75 and 100 Gm. (i. e. 0; 1.0; 1.5; and 2.0 Gm. per Kg. for a Body Weight of 50 Kg.).[14]

	P	C	F	Calories	Difference in Calories	
(1)	*0.000	83.333	166.666	1833.327	76.25	(2)−(1)
(2)	25.000	70.208	152.916	1757.076	76.25	(3)−(2)
(3)	50.000	57.083	139.166	1680.826	76.25	(4)−(3)
(4)	75.000	43.958	125.416	1604.576	76.25	(5)−(4)
(5)	100.000	30.833	111.666	1528.331		

"*No. 1 is hypothetical and could only be considered as the nonprotein fraction of a larger combination."

"High-Fat" Diet of Newburgh and Marsh

In 1920 there appeared a report of a system of dieting which introduced a new principle and appeared to be in conflict with some of the principles which were regarded as axiomatic. This was the high-fat diet of Newburgh and Marsh.[16] In a report which dealt with a series of seventy-three cases and using what appeared to be an unusually high percentage of fat, they found that acidosis did not develop in any of the series, although the diabetes in most cases was of the severest type. All cases remained sugar free during treatment. In addition to the high percentage of fat in the diet, the protein content was small and so arranged as to contain .66 grams of protein per kilogram of body weight, a quantity which they demonstrated was sufficient to establish nitrogen equilibrium.

> "The conditions necessary for the establishment of nitrogen balance at this low level are several. Chief among them is the presence of sufficient total calories in the ingested food; there must be enough fat or carbohydrate in the diet to supply all the body needs for heat and energy, so that the protein may be used only for restoring body tissue. The protein-sparing qualities of carbohydrate and fat were discovered by some of the earliest students of metabolism, and it is well known that carbohydrate is the more efficient of the two in sparing protein, though in a mixed diet fat may replace carbohydrate in isodynamic quantities. In spite of this difference in the effectiveness of the two foodstuffs, the ability of fat to spare protein cannot be doubted."[15]

The high fat content of the diet gave a total number of calories which would have been difficult to obtain with carbohydrates in quantities not sufficient to cause glycosuria or with protein, and in the case of some of the younger patients the capacity for work was "astonishing."

Newburgh and Marsh also take into account those principles of metabolism which have been stated, with reference to the efficiency of

fats in sparing protein and of their equality with carbohydrates for this purpose; that carbohydrates may not be entirely replaced by fat and that as long as a supply of fat remains in an animal the same quantity of fat will be burned, being drawn from its diet or the supply of body fat. They find from a study of their cases that as the caloric value of the diet is increased by the addition of fats, the protein catabolism is diminished and it is evident that fat is highly efficient as a "protein sparer." If the caloric value of the diet is too low for the energy requirements, the increased nitrogen metabolism may give not only increased nitrogen in the urine but also glycosuria (glucose from protein; in one of their cases the glucose from this source amounted to 20 grams), a condition to be avoided by the addition of more calories. Thus, by lowering the protein diet, the amount of carbohydrates may be increased and by limiting the endogenous protein metabolism, further carbohydrate may be added. The addition of fat to the diet accomplishes these ends and maintains nitrogen equilibrium. Newburgh and Marsh, in view of the known facts of protein and carbohydrate metabolism, also suggest the fallacy of fasting:

> "These facts show a fallacy of starvation in the treatment of diabetes. During the period of starvation, a subject well supplied with body fat burns this fat, and burns no less than he would if the fat were given him in the diet. This was demonstrated by Voit's experiment on a dog, which has already been mentioned. In the case of the fasting lean diabetic, however, who cannot burn glucose, and whose supply of body fat is low, energy and heat are developed almost entirely by the combustion of protein. Destruction of body protein produces glucose exactly as much as does combustion of ingested protein. In the more severe grades of diabetes this is a factor of prime importance. Such patients become sugar free sooner if they are allowed a little carbohydrate and a relatively large amount of fat than they do if starved. . . . The same undesirable production of glucose from body protein occurs to a lesser degree when an under nutrition diet is used in the treatment of diabetes mellitus. If the total calories fed the patient are not sufficient to supply caloric requirement, body protein is broken down and glucose is produced. If an effort is made to supply enough protein in the diet to compensate for this excessive destruction of body protein, the ingested protein is a source of glucose. Just in so far as the carbohydrate burning function of the patient must be used for the combustion of glucose derived from protein, just so much more must his carbohydrate intake be limited. Fat offers the best agent in the diabetic for the sparing of protein, either endogenous or exogenous."[15]

Their routine is as follows:

> "When a patient enters the clinic, he is placed on a diet containing from 900 to 1,000 calories, of which about 90 gm. is fat, 10 gm. is protein and 14 gm. is carbohydrate. After the patient has been sugar free for one or two weeks, his diet

is increased to about 1,400 calories, of which 140 gm. is fat, 28 gm. is protein and from 15 to 20 gm. is carbohydrate. In the cases of small individuals this diet is sufficient for prolonged use, and some of them are discharged with instructions to continue it. For larger persons, after another period of trial, a second increase is made, reaching 1,800 calories, containing 170 gm. of fat, from 30 to 40 gm. of protein, and from 25 to 30 gm. carbohydrate. Further additions up to 2,500 calories may be made to suit individual cases."[16]

Newburgh and Marsh as a result of their observations in the treatment of seventy-three cases reported in 1920 conclude:

"Patients with severe diabetes, as a class, do not remain sugar free on the usual high protein diet unless the total energy intake is kept so low that incapacity from starvation results. The only satisfactory diet is one which will keep the diabetic sugar free, which will prevent the occurrence of serious acidosis, which will maintain nitrogen balance and which will make it possible for him to resume the ordinary activities of life. With these four points in mind, we studied the effect of a high fat, low protein, low carbohydrate diet in the treatment of diabetes. Our experience with this type of diet in the management of seventy-three diabetics has convinced us that it is capable of fulfilling these four specifications."[16]

Maignon[17] in France has also used a "high fat" diet and observes that when fat is eaten by diabetics the effect is to decrease the amount of protein drawn from the tissues and to reduce the nitrogen content of the urine. He prescribes a diet rich in fat and oil, and to guard against acidosis gives sodium bicarbonate concurrently.

Diabetes in Children

Diabetes in children has always been recognized as grave. The supposition of Falta (see page 188) relative to a congenital defect of the pancreas is borne out by many of the facts. Morse says:[18]

"It was formerly supposed that almost all of the cases in childhood were of the severe type, but more recent studies have shown that the two types are about equally common in the beginning, with a greater tendency for the mild to change to the severe than in later life. About two-thirds of my own cases were, however, of the severe type."

The duration of life is probably about three years. Von Noorden gives the average duration of his cases, developing before the seventh year and in which the disease was diagnosed after development into the severe type, as from one and a half to two years. The prognosis is usually grave. Allen states that "The ultimate outcome of youthful diabetes is still uncertain" and von Noorden "With few exceptions, diabetes in childhood knows no cure, no matter how mild it may appear in the beginning and how gradual its development in the first months or even years." Reports of recovery of diabetes in children are, how-

ever, not entirely rare. Riesman, at a meeting of the Association of American Physicians at Washington in 1915, described a mild type of diabetes in children, not progressive, which remains either stationary or ends in apparent recovery.

The treatment is the same as in adults, but it should be borne in mind that acidosis develops much more readily in children and in view of their greater energy requirements and the importance of carbohydrates in preventing acidosis the rigid restriction of the diet, particularly of the carbohydrates, is dangerous. It would seem that in these cases more than the usual reliance should rest upon the direct substitutive and stimulative effects of pancreas therapy.

Direct Therapy

Pancreas Therapy—A Direct Aid to Impaired Pancreatic Function

It is evident from the conception of diabetic pathology that dietetic treatment, no matter how well selected and balanced, simply brings the work of the islands of Langerhans within the limits of their functional capacity and permits of a possible gradual, spontaneous upbuilding of this capacity, but it in no way exercises any specific therapeutic effect in restoring the injured islet tissue. The effective treatment of diabetes, therefore, will include measures for rebuilding the diseased insular apparatus and increasing its internal secretion. "Any positive means of augmenting the endocrine pancreatic function, even by a little, would give therapeutic results far surpassing those of the negative plan of sparing the function by diet."[19] Most of the recent research has been devoted to this phase of diabetic treatment. As a defect of an endocrine tissue, the treatment of diabetes follows the general principles of organotherapy in other endocrine diseases. The active principles found in the pancreas are the only known substances that act through the pancreas in substituting for its failing internal secretion and in rebuilding its active secreting tissue. In experimental diabetes it has been shown that if as little as 1/5 to 1/8 the entire gland is left in the animal a mild diabetes develops; if a lesser amount is left a rapidly fatal type ensues; and if a larger amount is left it is sufficient to prevent the appearance of diabetes. The small proportion of pancreas sufficient to carry on the normal carbohydrate metabolism suggests that a relatively small impetus from pancreas therapy in raising the functional capacity of the islet tissue would be sufficient to change a case from diabetic to non-diabetic, *i. e.*, to prevent glycosuria and enable the patient to metabolize a normal quantity of carbohydrate food. Actually this has been found to be the case.

The investigations of MacLeod, Banting and Best,[20] using a specially prepared pancreas preparation, have brought the attention of the entire profession to the remarkable results of pancreas therapy.

Insuline in Treatment

The value of insuline itself in the treatment of diabetes mellitus and the effects it exerts upon the diabetes pathology are now fairly well understood. Insuline is not a cure for diabetes. There is no evidence that its continued administration results in permanently increasing the carbohydrate tolerance or

capacity of the organism for the utilization of sugar. It can not be administered orally, but must be given hypodermatically. It is a powerful drug and in overdose gives rise to violent symptoms, convulsions, etc. (which may be controlled by giving sugar). The diet must be carefully adjusted to the insuline dosage.

For the treatment of coma, diabetic gangrene, acidosis and the emergencies of diabetes insuline has earned an enduring place. For the routine treatment of diabetes of the mild or moderately developed type, extending over years, the daily or twice daily injection of an expensive product has failed to meet the requirements. Oral administration appears to be the only satisfactory method for this long continued treatment in the home. Numerous extracts have been prepared for oral administration and have proved successful in reducing blood sugar and in correcting the disturbed carbohydrate metabolism. Berkeley,[21] Wallis,[22] Achard[23] and others have prepared extracts which gave good results clinically, and Banting and Best[11] and Murlin[8] have given experimental evidence of the value of such extracts by administration through the stomach.

No pancreas preparation, however, has received as extensive clinical trial as Trypsogen. Its use has extended over a long period of years and the reports of its use show that it aids in the utilization of sugar by the body, depresses a relative adrenal hyperfunction, lessens polyuria, decreases glycosuria and often causes its entire disappearance, aids in reestablishing normal carbohydrate metabolism and exerts a remarkable action in improving the subjective symptoms of diabetes. As a consequence of the action of Trypsogen in augmenting the internal secretion of the pancreas and in improving sugar utilization, it has been found that the necessary dietary restrictions are less rigid in diabetes treated with Trypsogen and that the tolerance for carbohydrates is raised more rapidly. Trypsogen has been used for a period sufficiently long to warrant the conclusion that it is a dependable and necessary part of the routine treatment of diabetes mellitus.

Summary of Foregoing Principles of Diabetic Treatment

1. Determination of the quantity of glucose that can be utilized without waste and adjustment of the diet below this quantity, effecting a cessation of glycosuria and bringing the blood sugar to an approximately normal figure.

2. By means of weighed and calculated quantities of fat, carbohydrate and protein, adjust the diet to meet the caloric requirements and establish nitrogen equilibrium.

3. Adjust the ratio of fatty acids (from fats and proteins) to glucose to create a favorable ketogenic balance, in order to prevent acidosis.

4. Avoid a diet too high in either fats or proteins, for fat yields in metabolism 90% of fatty acids capable of causing acidosis, and protein yields 58% of glucose capable of causing a carbohydrate excess, with glycosuria and hyperglycemia, as well as 46% (calculated as ketogenic acids) of fatty acids capable of causing acidosis. Newburgh and Marsh,

although using higher fat percentages than were formerly thought possible, recognize the necessity of adequate carbohydrate diets.

> "While a partial replacement by fat of carbohydrate in a low protein diet will not affect the protein metabolism, complete withdrawal of carbohydrate and substitution of fat will not permit the establishment of nitrogen balance at low levels. Fat alone will not decrease the amount of nitrogen found in the urine of a fasting animal. It is generally believed that fat in a low protein diet loses part of its effectiveness when the carbohydrate calories fall below 10 per cent. of the total calories."[15]

5. Instruct the patient in the principles of diet, methods of weighing food, making reports for the physician, conserving his energy and the technic of urinalysis, an explanation of the dangers of infections from small wounds, the necessity for regulated exercise and mental repose.

6. Any glycosuria, particularly if there is a tendency to persist, should be regarded as diabetes.

7. Meet any indications of impending acidosis promptly. The work of Newburgh and Marsh has demonstrated the value and safety of larger quantities of fat than has hitherto seemed wise, but it would appear good practice in all cases which show a tendency to acidosis to make the fat intake at least as low as those values calculated by Woodyatt.

8. Fasting may prove of value in rendering the urine sugar-free, preliminary to the determination of glucose tolerance or as a part of routine treatment. It is safer, however, in the practice of experts and with observance of the principles of diet described herein is probably necessary in general practice only rarely.

9. Routine treatment with Trypsogen. The desirability of direct treatment is now generally recognized and Trypsogen furnishes a means of directly affording aid to the impaired function of the pancreas, and aids in rebuilding and restoring to a normal condition.

Diabetes in General Practice

Many of the methods of the expert, in laboratory analyses and calculations of food values, are not possible for the general practitioner and the majority of diabetics are necessarily treated in accordance with general principles rather than by carefully calculated dietaries. In following out those general principles which are accepted as sound, the physician may bear in mind the following:

1. The urine should be made sugar-free and the diet adjusted so that it will remain so, but it should be remembered that it is not *sugar per se* that is harmful to diabetics but the inability to utilize it.

2. "The fasting procedure is applied with safety only in the hands of the expert."[24] At a discussion of the Association of American Physicians, May 9-11, 1916, on the "Starvation Treatment of Diabetes," Dr. Abraham Jacobi, of New York, said:

> "The starvation treatment of diabetes is very satisfactory to the experimental doctor, but what happens to the patient? I

> have seen patients with 5 or 6 per cent. of sugar go along in satisfactory health for five or ten or even twenty years. I have also seen starved patients, emaciated, suffering with cerebral anemia, complaining bitterly of other symptoms of nerve exhaustion, and now they are dead. They would not be dead if they had not been starved. Are not those living patients with glucose in the urine better off than those who died?"

The urine usually becomes sugar-free on a reduced diet. "Ordinarily, a diet consisting of one gram of carbohydrate and one gram of protein per kilogram of body weight, continued for a day or two, orients us definitely as regards the severity of the case in hand."[24]

3. The maintenance diet which the patient will regularly receive will be made up of as much carbohydrate (preferably as green vegetables) as can be given without the appearance of sugar in the urine (using Benedict's test). Joslin says:[2]

> "I cannot escape from the impressions: (1) that in those countries where the diet consists largely of carbohydrate, the diabetes is mild; (2) that the diets of those diabetics who live longest, whether they show sugar or not, are those whose carbohydrate has never been long reduced to a very low quantity."

4. Protein will be given in quantities just sufficient to establish "nitrogen equilibrium." Clinically this is determined by observing when loss of weight ceases (usually 60 grams — about 2 oz. — per day is enough). Uncooked lean meat contains an average of 20% protein, so that 10 oz. of lean meat per day would furnish the ordinary requirement if protein in no other form was given. Fish contains slightly less protein than meat. It should be remembered that the more protein (meat, fish, etc.) given, the more the other classes of foods must be reduced, as protein itself gives rise to sugar.

5. Fats can be given in larger quantities than has hitherto been regarded as safe. If much fat is given, however, the protein should be low and the carbohydrates in large enough quantities to insure oxidation of the fatty acids (a ratio of 1.5 grams fatty acid to 1 gram glucose)

6. The total quantity of all food should be reduced to a level which will just supply the energy requirements.

7. The quantities of fat, carbohydrates and protein should be approximately the same for each meal.

8. The patient must be instructed to make his habits of life (muscular efforts) correspond to his reduced energy production, to avoid scratches and injuries to the extremities, with possible infection, and as to the necessity of adhering to the prescribed diet.

9. Trypsogen should be given in a dosage of 2 tablets after each meal, and the daily amount may be increased by 1 tablet a day until the patient is taking 6 or 7 tablets three times daily. In diabetes complicated with albuminuria, Trypsogen Without Gold and Arsenic should be used.

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PART III

CHAPTER III

ASTHENIA, HYPOTHYROIDISM, HYPOADRENIA, SENILITY

The treatment of general debility and of states of lowered vitality in which no demonstrable pathologic process is present has always been a stumbling block for the general practitioner. Organotherapy now offers a solution to this problem in that it introduces substances which directly stimulate cell metabolism and raise metabolic rate. The successful treatment of these conditions has, therefore, become possible. Of course, the pathology in these conditions is comparatively unknown — that is, there is no structural defect, but a functional derangement due to glandular deficiency. Following extended illness, states of exhaustion and the infections, and occurring as a result of the burdens and conditions imposed by various walks of life, these states have been treated by "tonics," "alteratives," etc. Only too frequently the "tonic" has been some substance designed to increase appetite and digestive capacity, in the belief that lack of strength results from some primary lack of nutrition. The following discussion, it is hoped, will indicate a better therapy.

ASTHENIA

Asthenia is a symptom characteristic of almost all disease, both infectious and metabolic, and may also, and frequently does, manifest itself as the principal or only symptom in conditions in which there is no demonstrable pathology. It constitutes one of the commonest conditions that the general practitioner is called upon to treat and includes patients recovering from definite illness, prolonged infections and states of general lowered vitality. For these reasons a rather extensive investigation of the causes of asthenia and the general nature of the conditions under which it appears is of more than ordinary interest to the physician. Asthenia, as here used, is but slightly, if any, more inclusive than the term "myasthenia." It is mere weakness, the "run-down feeling," for which some effective treatment is necessary. The train of associated symptoms, undue fatigability, cardiac insufficiency, feeble pulse, arterial hypotension, arrhythmia, bradycardia, vasomotor disturbances, cold extremities, etc., which together make up a complete clinical picture of debility, will be considered in the following discussion of hypoadrenia. Asthenia may occur, however, as a result of disturbances of both the pituitary and thyroid, as well as of the adrenals. In the frequently encountered clinical conditions characterized by lowered basal metabolism and lessened functional activity of the acceleratory group of endocrine organs, asthenia is conspicuous. The energy production of the organism and the cell metabolism are at fault and the subjective symptom, asthenia, arises.

Sejary[1] distinguishes between asthenia due to suprarenal insufficiency and those due to other causes. The adrenal type is characterized by rapid muscle exhaustion and fatigability, whereas other types show a diminution of muscular force but not a rapid exhaustion. According to Sejary, it is as yet unproved that any other asthenia of endocrine origin can present this special type of rapid exhaustion of muscular force. Asthenia forming a part of the Erb-Goldflamm syndrome may be mentioned as a variety occurring independently of the endocrine system, although even this has been suggested as of adrenal origin. Harvier says[2]:

> "Certain cases of myasthenia which are included in the syndrome of Erb-Goldflamm, characterized by muscular asthenia (weakness of the muscles, tendency to be easily tired), either diffuse or limited to certain muscles of the face, are probably due to some adrenal disturbance. They improve under adrenal medication, alone or combined with thyroid or pituitary extract."

Sejary, however, differentiates it from the adrenal type by the paralysis of the oculomotor and facial muscles, and those of the neck, conditions not present in the adrenal type, which shows no especial predilection for the muscles innervated by the cerebral nerves.

Pathology of Fatigue

A study of the fatigue process gives some aid in understanding the nature of asthenia, which is the conscious sense of muscle inefficiency. Many experimental studies of fatigue have been made and at least something is known of the conditions in which it arises. It seems fairly well established that an accumulation of the waste products of catabolism, "fatigue substances," are directly concerned in the condition. In some cases a second possibility is present — that of a too rapid consumption of the material necessary for the work of muscle contraction — but this need not be considered here. Ranke made the first comprehensive investigations of fatigue pathology and suggested the name "fatigue substances" for those compounds which, when present in sufficient concentration, inhibit muscle contractions. He showed that extracts of fatigued muscle, when injected into the circulation of a fresh animal, artificially produced fatigue, whereas extracts of fresh muscle substance (not fatigued) gave no such results. That such substances are actually formed and are largely responsible for muscle fatigue seems fairly certain from the nature of the various experimental results and from clinical experience. Such substances produced in one set of muscles affect not only that particular set but, diffused through the circulation, definitely lower the efficiency of other muscle groups and cause the general malaise and psychic dullness incident to fatigue of the organism as a whole. Lactic acid appears to be chief among these fatigue substances and in muscle preparations fatigue may be produced by bathing or perfusion with lactic acid solutions. Aqueous solutions of muscle previously exhausted to the point of fatigue also reduce the excitability of the muscle preparation and induce the fatigue condition. In experiments in which the muscle is not cut off from its circulation and in which the accumulation of these substances is more difficult, fatigue is much less readily

produced than in those isolated preparations in which the conditions for accumulation are ideal. In either class of preparations the fatigue may be relieved by flushing with normal salt solution.

The action of these fatigue substances may be either in the muscle itself or in the myoneural junction — the receptive substance — of the nerve ending: less likely does it appear that they act through the nerve tracts themselves.

What conditions permit the accumulation of the toxic wastes responsible for asthenia and the fatigue syndrome? Chief among these is lack of oxygen and the resulting state of suboxidation and lowered metabolism.

> "It seems more probable that we are dealing here with two stages of one process and that in the muscle under normal conditions (that is, richly supplied with oxygen) the first chemical change is one of disintegration, leading to the formation of lactic acid (and probably other substances), and that this is followed by a process of oxidation, in which all the products of the first stage are converted into CO_2, which can be rapidly eliminated from the muscle. If the supply of oxygen is deficient, the products of the first stage remain in the muscle, giving rise to the phenomena of fatigue."[3]

The effect of oxygen gas in relieving fatigue and restoring the irritability of muscle preparations previously exhausted is evidence of the influence of oxygen in preventing the onset of the fatigue syndrome. With a free supply of oxygen, the excessive accumulation of lactic acid, with its inhibitions to muscle contractions, does not take place. Lactic acid is formed as a result of the work performed by the muscles and may be an intermediary product of sugar metabolism. A certain acid concentration appears to be necessary for contraction, however, and it is probable that even in ideal conditions of oxidation the lactic acid is not finally and wholly oxidized but rather is synthesized into the substances from which it was formed. Suboxidation, therefore, causes fatigue through permitting *excessive* accumulation of the acid.

> "In the process of recovery which follows the activity of muscle when it is allowed to rest, it is found that the lactic acid disappears provided a supply of oxygen is available. Since at the same time carbon dioxide is set free from the muscle, one might suspect that the disappearance of the lactic acid is due to its being oxidized to carbon dioxide and water. This, however, cannot be the case, for it is known that after the repeated fatigue and recovery of an isolated muscle the total quantity of lactic acid which may be extracted from it is undiminished. In other words lactic acid does not disappear from the muscle during rest, but is restored to the condition in which it occurred before contraction took place. Further evidence that lactic acid is not oxidized is afforded by the fact that the disappearance of 1 gram of lactic acid from fatigued muscle is accompanied by the production of 450 calories of heat, whereas the oxidation of 1 gram of lactic acid would

set free 3700 calories. Apparently the oxidation of some other substance is necessary in order to restore lactic acid to the precursor condition, and to replace the potential energy lost in the contractile process, and in the course of the oxidation of this substance — carbon dioxide is liberated and heat is given off. The nature of the substance oxidized is not definitely known, but it is presumed from the high respiratory quotient of muscular work that it is chiefly carbohydrate."[4]

Adrenal Influence

Asthenia is undoubtedly the most conspicuous and characteristic symptom of adrenal insufficiency, and the function of epinephrin in the maintenance of voluntary muscle efficiency is very striking. Cannon, Gruber, Fellows and others have shown that epinephrin increases the contractility of the voluntary muscles and diminishes the tendency to muscle fatigue. Gruber reached the following conclusions[5]:

"In the fatigued unaltered nerve muscle adrenalin may increase the height of muscular contraction by a twofold action, by improvement of the blood supply (vasodilation) and by its chemical action upon some substances in the muscle.

"In a muscle in which the nerve is cut and stimulated, adrenalin in small doses, however administered, does not better the circulation and must therefore produce its effect of increasing the height of muscular contraction by its chemical (specific) action alone.

"The following three processes which normally go on in the muscle may be greatly accelerated by adrenalin and it is not improbable that one or all of these will finally prove to be the way in which adrenalin produces its effects:

"1. The conversion of glycogen into sugar.

"2. The reconversion of lactic acid into sugar (transformation of fatigue products).

"3. The oxidizing of lactic acid into carbon dioxide and water (destruction of fatigue products)."

Gruber and Kretschmer[6] in experiments upon cats found that:

"Adrenalin (0.5 to 1 c. c. of 1:1,000 solution) counteracts the induced fatigue produced by the perfusion of fatigue substances, such as sarcolactic acid, lactic acid and acid potassium phosphate, through the muscle in identically the same way as it does the fatigue produced normally in active muscles."

Hartmann[7] investigated the effect of epinephrin upon muscular activity and has shown a very definite relationship between epinephrin output and muscular response. He finds that in normal animals there is an increase in epinephrin output during exercise, which output is greater in proportion to the length and vigor of the exercise. This increased epinephrin output persists after the exercise ceases, the duration depending to some extent upon the amount of work performed. Hartmann also found that intramuscular injection of adrenalin improved the output of work in many normal cats and in cats with epinephrin deficiency, and that an animal can go further and travel faster when

there is an increase in the epinephrin output during exercise. Hartmann makes an interesting explanation of the so-called "second wind" of athletes, which he relates to the increased efficiency resulting from epinephrin. He believes that epinephrin is an important factor in the development of "second wind" or that state of increased efficiency which takes place after a condition of exhaustion has apparently developed.

In investigations made by Hartmann, Waite and Powell[8] they came to the conclusion:

> "Our results seem to indicate that epinephrin plays a very important rôle in increasing muscular work and delaying the onset of fatigue."

The influence of epinephrin seems to be due to a direct specific influence upon the muscle cell and this conclusion has been reached by various investigators. Gruber[9] finds that, while in some of the experiments the increased height of the muscular contraction may be accounted for by increased circulation through the muscle, there are specific effects in eliminating fatigue. The manner in which the specific action is accomplished is unknown and may be due to the neutralization or destruction of the fatigue products, the rapid formation of more available energy, or to some toxic action increasing the excitability of the muscle.

It has been suggested by MacLeod (see above) that the oxidation of some substance, presumably carbohydrate, is necessary to prevent the excessive accumulation of lactic acid and to restore it to the precursor substance, a mode of action also suggested by Hartmann (transformation of fatigue products). There has been much evidence to show that the adrenals are important factors in sugar metabolism (Bierry, Malloizel, Cannon, Porges) and, although such influence is minimized by some, the evidence is very suggestive of an action in sugar metabolism which, in part at least, accounts for the epinephrin effect in relieving fatigue.

> "The asthenia which dominates the clinical picture of adrenal insufficiency may be explained by the undoubted fact that adrenalin presides over carbohydrate metabolism. As for the latter view, it is true that adrenalin regulates the deposit of glycogen in the liver and its transformation into glucose; if adrenalin is deficient, carbohydrate metabolism is interfered with and muscular action is rendered impossible."[10]

It should be mentioned, too, that the effects of the cortex, which are important in producing other symptoms of hypoadrenia, may also be a factor in producing the asthenia. The evidence, however, points strongly to the epinephrin as the essential factor.

In marked muscle fatigue the quantity of epinephrin in the adrenals themselves is much reduced and in the light of Hartmann's observations above this appears to indicate that in the maintenance of muscle efficiency, following the demands of excessive contraction, all the available epinephrin is consumed, and fatigue develops when the store has been exhausted and epinephrin is no longer available. Vacuole formation in the cortical portion is also noted and indicates some function of this portion of the gland in muscle work.

HYPOADRENIA

Hypoadrenia or suprarenal insufficiency has been described under various names and divided into various classifications, for the most part depending upon the duration, and the extent and character of the symptoms. In 1899 Sergent, in association with Leon Bernard, made what appears to have been the first description of a case of suprarenal insufficiency not Addisonian in character. Addison's disease is an extreme example, representing the upper limit of suprarenal insufficiency, and the milder cases of clinical hypoadrenia, the existence of which has been challenged by some workers in experimental physiology and pathology, represent the lower limit.

The symptoms of actual extirpation of the adrenals include rapidly developing asthenia (myasthenia), convulsions, psychic depression, cardiac weakness, lowered temperature and blood pressure, dyspnea, etc. In some of the acute forms of suprarenal insufficiency (suprarenal hemorrhage) symptoms approximating these may be observed. The onset is sudden and the course rapid and fatal. Acute gastrointestinal symptoms — vomiting, diarrhea, etc. — may be marked. In Addison's disease the asthenia is an outstanding symptom and there is also another perhaps equally characteristic, the discoloration or bronzing of the skin, that is not apparent in other forms of insufficiency. The asthenia has been described above. Epinephrin appears to play an important part in muscle work and fatigue, and there is much evidence that the myasthenia at least is due to deficiency of this substance. It should be made plain that the evidence in favor of epinephrin deficiency as a cause of the symptom asthenia is much stronger and generally less open to question than as a cause of low blood pressure and other symptoms of hypoadrenia, in which physiological research at least seems to have shown that epinephrin does not play such an important part. The blood pressure is characteristically low. It is not possible to state just what defect of the suprarenal glands is responsible for this condition, but it forms a fairly constant feature of hypoadrenia and there can be no doubt but that the suprarenal medulla or cortex, or both, are essential in the maintenance of vascular tone and circulatory efficiency. Feeble heart action is a concomitant of the low pressure and is explicable in the light of the known stimulatory action of epinephrin on cardiac muscle and the lack of tonicity resulting in all contractile cells as a result of the accumulation of the products of lowered metabolism. Josué[11] described a special type of cardiac affection — cardiac asystole — in which suprarenal insufficiency appeared to be the cause. There were cases with demonstrable hypertrophy and both systolic and diastolic pressures were constantly low, and three of the four cases showed marked arrhythmia and auricular fibrillation and the symptoms of dyspnea, pulmonary and hepatic congestion and edema. Although histologic examination showed a comparatively normal condition of the cardiac muscle fibres, the suprarenals were in all the cases very small, degenerated and giving every evidence of much decreased functional activity in life. Metabolism in general is reduced, an effect that may be due to either the impaired function of the cortex or medulla. An appreciable reduction in the blood sugar takes place.

Gastro-Intestinal Symptoms

The gastric, intestinal and digestive symptoms observed in extirpation experiments are evident in lesser degree in the milder clinical forms, and vomiting, diarrhea, anorexia, dyspepsia, etc., are common. Loeper[12] has described a type of indigestion caused by suprarenal insufficiency, characterized by gastric distress and constipation, the pain arising in from half an hour to two hours after eating. This is attended by asthenia, low blood pressure and general depression, all of which improve with the improvement in the suprarenal factor. An interesting and not satisfactorily explained association of gastric and gastro-duodenal ulcers with disease of the adrenals may be noted. Silvestri[13] concludes that these are chiefly the result of the predominance of the vagus system and that when there is a good balance of the endocrine system these ulcers are not formed. The vagus influence may be accentuated by stimuli from the sex glands, for castration at pregnancy depresses the vagus activity and cures the ulcers, while partial or total removal of the suprarenals causes gastric and duodenal ulcers. It would seem that the experimental suprarenal insufficiency produced by Silvestri may produce ulcers by removing the antagonistic effects of the sympathetic system ordinarily stimulated by the suprarenals.

In experimental insufficiency, effects upon the body temperature are evident. Scott[14] found that in suprarenal insufficiency, amounting practically to suppression, there is a decrease of heat production and death. In less severe injury and consequent lesser insufficiency (in cats) there is a "profound effect upon the calorific mechanism, characterized by a significant increase in heat production." Probably in the clinical types marked variations in temperature are complicated with abnormal function of other endocrine glands.

Types of Hypoadrenia

Sajous classifies hypoadrenia as:

1. Functional hypoadrenia,
2. Progressive hypoadrenia,
3. Terminal hypoadrenia,

a classification which, for the practical purposes of clinical medicine, is as good as any proposed, although numerous others have appeared.

Effects of Infection, Toxemia and Defective Diet

The adrenals show marked changes following acute infections, and nutritional disturbances and chronic infections as well are accompanied by changes in the glands. McCarrison found that the functional activity of the adrenal glands is dependent on the quality of the food,[15] and that in animal experiments the adrenal glands enlarge in consequence of qualitatively deficient food. He finds as a result of his studies that: "An intimate relationship exists between the adrenal glands and the metabolic processes of the animal organism." Particularly following influenza is the involvement of the adrenals very common and the pronounced prostration characteristic of this condition seems to depend upon this adrenal factor. Hypoadrenia is also characteristically found following typhoid fever, pneumonia,

diphtheria, scarlet fever, malaria, tuberculosis, etc. This is the "terminal" hypoadrenia of Sajous, described by him as due to exhaustion of the glands during the acute febrile period of the infection. The adrenals appear to be peculiarly susceptible to infection or toxins of any kind, and continued irritation of toxic substances may result in a condition of permanently lowered functional activity.

The relation of the adrenals to the emotions, the "emergency" theory of Cannon, seems to bear application to certain types of insufficiency arising as a result of psychic causes — intense emotion, etc. A class of cases common during and after the war is of this kind. Asthenia, low blood pressure, pronounced psychic symptoms, circulatory disturbances and inability to assemble the bodily resources for rapid, unusual demands, appear to be due to adrenal insufficiency resulting from previous heavy and overwhelming demands upon the adrenal apparatus. Satre has described such conditions in soldiers and believes the mental and physical overexertion of the soldier leads to exhaustion of the endocrine and other organs. Shock he believes is *per se* largely a condition of adrenal insufficiency.

Functional Hypoadrenia

Definition of Functional Hypoadrenia

"Functional hypoadrenia is the symptom complex of deficient activity of the adrenals, due to inadequate development, exhaustion by fatigue, senile degeneration, or any other factor which, without provoking organic lesions in the organs or their nerve paths, is capable of reducing their secretory activity. Asthenia, sensitiveness to cold and cold extremities, hypotension, weak cardiac action and pulse, anorexia, anemia, slow metabolism, constipation, and psychasthenia are the main symptoms of this condition.[16]

This form of hypoadrenia is encountered at four periods of life: infancy, childhood, adult and old age, and includes the asthenias of these periods usually described as resulting from "weakness or exhaustion." (Sajous.) This type may be due to a congenital underdevelopment of the adrenal tissue, a conception which has found frequent expression in the literature and which might account for an adrenal insufficiency type.

> "There is a very large, not very well defined, but very important field, which is characterized by so slight a degree of suprarenal insufficiency that it is called *myopragia congenita* of the suprarenals. It is constitutional, hereditary or acquired through infection or toxins. This myopragia, whether constitutional, congenital, hereditary or acquired, may have for its pathological basis a hypoplasia or simply a functional insufficiency of the suprarenals, which has been caused by some dystrophy resulting from a disease in the ascendants, especially tuberculosis and syphilis. According to Wiesel, this condition is caused by the status thymico-lymphaticus and with it is often associated the syndrome of constitutional vagotonia, eosinophilia, exudative diathesis, and we are led to believe

that the basis of these conditions is a constitutional suprarenal insufficiency." (Pende.)

Functional hypoadrenia may be self limited and undergo spontaneous recovery. The removal of the excessive demands upon the function is usually followed by some improvement in the symptoms. The mental attitude is frequently characteristic and is one of indecision, lack of initiative and tendency to melancholia.

Experimental physiology has not contributed any brilliant results in establishing a condition of artificial hypoadrenia, a fact which has led to some physiologists adopting a somewhat skeptical attitude toward the clinical varieties of adrenal insufficiency. The criticism arising from this class of workers has shown such a disregard for the facts of clinical medicine, and the limitations of the experimental method are so apparent, that it fails to carry conviction or bear the importance which properly interpreted physiological investigation should. In a reply to criticism of this kind, Sergent[17] gives a comprehensive review of the clinical views of the condition, following the first described case (his own) in 1893. Sergent disposes of the criticism, that clinicians generally attribute the symptoms of suprarenal insufficiency (including Addison's disease) to insufficient epinephrin production, by showing that at the time of the first description of this condition epinephrin was unknown and that clinical views since (including his own) have generally regarded the condition as an insufficiency of the whole gland. Pende clearly recognizes the influence of the whole suprarenal in giving rise to the symptoms of insufficiency:

> "The cortex and medulla are so intimately connected that it is not possible to imagine functional efficiency of one without that of the other. This intimate connection may be traced all the way up in the scale of the vertebrates, being more and more intimate and complicated as we pass from the lower to the higher. In the lower animals, their functions are perfectly distinct, but as we approach the mammalia they become more and more inseparable. It seems as if we were justified in inferring that the syndrome of medullary insufficiency is not alone caused by the lack of adrenalin in the blood. Rather are we inclined to think that many of the symptoms of adrenalin deficiency, which we find in animals that have been deprived of their suprarenals, are due to unknown but strictly necessary connections between the medulla and the cortex."

Sajous[18] also emphasizes the error of assuming that clinicians attribute Addison's disease to an epinephrin insufficiency. There seems little doubt but that the syndrome of suprarenal insufficiency — asthenia, hypotension, feeble and irregular heart action, vasomotor instability, gastric and other digestive disturbances, lowered metabolism, psychic depression, etc. — is due to insufficiency of both parts, cortex and medulla, as it has been shown in convincing manner that death in extirpation experiments is due to loss of the cortex, while total suppression of the epinephrin output is followed by impaired metabolism, for, al-

though numerous observers have shown that the concentration of epinephrin in the circulating blood is normally very small, even physiologists who have most critically examined the facts of the rôle of epinephrin in the organism do not deny a physiological function. "Small as the concentration of epinephrin may be in arterial blood, there is evidence that it may exert a certain action."[19]

That suprarenal insufficiency is due to an insufficiency of the whole gland is suggested by injection experiments using suprarenal extract, resulting in effects not obtainable with epinephrin. In the treatment of Addison's disease, an extreme case of insufficiency, the treatment is with whole gland and not by epinephrin. "Either the fresh gland or a glandular extract or the dried gland, all representing the whole gland, must be used to expect beneficial results, as shown by a personal study of 120 reported cases."[18]

Sergent has pointed out that both physiologists and clinicians agree that the suprarenals are indispensable to life, a conclusion reached by the methods of both fields of science, and that slowly developing disease of the glands is accompanied by well marked symptoms.

> "Alongside the syndrome of acute suprarenal insufficiency provoked by sudden and complete destruction of the suprarenal glands clinical observation therefore ranges syndromes of gradual insufficiency and ascribes them to progressive alteration of those glands, an alteration insufficient to suppress function totally, but quite pronounced enough to diminish it. Asthenia and hypotension are its cardinal signs. These two classes of syndromes constitute the principal clinical modalities of simple suprarenal insufficiency. When melanoderma is added, Addison's disease comes into being — a morbid complex formed apparently by a union of the symptoms of suprarenal insufficiency and those of pericapsular sympathetic irritation."[17]

It seems that the only uncertainty in connection with this syndrome, therefore, is in explaining the nature of the effects of the entire suprarenal gland, a problem which is as yet hardly touched.

HYPOTHYROIDISM

Hypothyroidism is of common occurrence in general practice and, as in moderately developed cases it presents a picture of general debility, rather than distinct and typical disease of the thyroid, it may conveniently be considered in connection with the other common cause of debility, hypoadrenia. It is of value, however, to first consider those cases of hypothyroidism which are typically and definitely recognizable as thyroid in character, cretinism and myxedema, as an adequate conception of these conditions, in which the numerous symptoms characteristic of thyroid hypofunction are well marked, facilitates recognition and understanding of the minor degrees of the condition in which only a few of the usual symptoms may be present.

Hypothyroidism in the young, when well marked, is termed cretinism and presents a clinical picture which is unmistakable and differs from minor degrees of hypothyroidism in forming a definite, well marked

clinical type. Some authors distinguish various conditions, such as "juvenile myxedema," and limit cretinism to a congenital condition. Thus McCarrison[20] states:

> "Cretinism is always congenital, whether endemic or sporadic. Cases of thyroid deficiency arising in the individual and due to nutritional or infectious causes should be clearly distinguished and designated as juvenile myxedema."

Cretinism, however, is generally used to designate hypothyroidism in the young and myxedema is applied to the same condition in the adult. As these are the usual connotations of these terms and as they appear to be thus firmly fixed in the literature, it seems wise to retain them.

Complete absence of the thyroid is rare (twelve cases were reported by Pineles). Cretinism may occur in two characteristically different types — sporadic and endemic.

Sporadic Cretinism Sporadic cretinism occurs in all parts of the world. Hereditary factors appear to play an important part and hereditary defective development of the thyroid apparatus has been suggested as explaining many cases of hypothyroidism, just as congenital underdevelopment of the adrenals has been described in hypoadrenia. Many such cases do not develop the characteristic symptoms of cretinism and, in fact, may exhibit few or no symptoms. They develop into the characteristic hypothyroid cases under added demands of various kinds upon their functional capacity. Cretinic symptoms may be apparent in earliest infancy or may develop during childhood. The female sex appears to be more often affected and, following the profound physiologic changes in the female organism at puberty and pregnancy, there appears to be a greater proportion affected.

In well marked cretinism and myxedema actual structural change in the thyroid is constant, varying from total absence of the gland (thyroaplasia, athyreosis) to varying degrees of degenerative change. The symptomatology is in general in direct relation to the extent of the tissue change, the fully developed cretin approaching a condition of thyroaplasia and the milder cases of hypofunction showing but small thyroid structural change. The gland may be enlarged, simple non-toxic hyperplastic goiter arising as a result of an effort to compensate for faulty functional activity, or the gland may be markedly reduced in size as a result of general atrophy. The growth is affected, particularly the skeletal system, resulting in the dwarfed condition so characteristic of cretinism. The low mentality is equally prominent. The cretin in marked cases has the mentality of an idiot and in less advanced degrees is stupid, "backward," and obviously below the normal. Facial expression is vacant and stupid. They do not behave normally at play. The skin is severely affected and may be thickened and wrinkled, and is usually dry. Mucous membranes and subcutaneous tissue show the myxedematous swelling. The fontanelles are late in closing or remain open. The skull varies from the normal and appears larger proportionately than the rest of the body. Characteristic depression of the root of the nose is said to be due to faulty development of the vomer (saddle nose). Anomalies of dentition are usual and the deciduous teeth develop slowly and may be retained. The myxedematous infiltration of the skin and

mucosa gives a swollen appearance to the lips and mouth. The mucosa of the nasopharyngeal cavity is hypertrophied, the tonsils are frequently enlarged, and adenoids are common. The sexual organs are frequently underdeveloped. Deafness and partial deafness are common, though an explanation of this condition is wanting. The cheek bones are prominent, metabolism is depressed, and temperature is low. Constipation is usual. The face is sallow, pasty and colorless; the tongue protrudes from the mouth and is thickened and furrowed; the nose flattened and saddle shaped. Enuresis, possibly due to infiltration of the tissue of the neck of the bladder, is a frequent symptom. The abdomen is characteristically protuberant.

Endemic Cretinism

When cretinism occurs as an endemic disease the condition varies considerably from the sporadic variety and it has been held that endemic cretinism or cretinic degeneration is not thyroidal in origin, but is a general degenerative process involving the thyroid with the other organs of the body. Whereas sporadic cretinism is a clinical picture of advanced hypothyroidism, the endemic variety presents some symptoms and signs not explicable in such terms. Falta[21] states:

> "There is as yet no agreement as to the question whether the manifold manifestations of the cretinic degeneration are called into existence only by the mediation of the strumous degeneration of the thyroid gland, or a part of these are directly produced by the strumous noxus and thus are co-ordinate with the struma."

The general symptomatology of the endemic form shows much greater variety and less adherence to type than the sporadic, and in some localities individuals affected show the most marked variations in type. Endemic cretinism is well known in some localities of the world and an appreciable number of the population are affected by it. Practically all the symptoms of the sporadic variety may occur. Nervous involvement is more common and deaf-mutism is usual. "Eighty per cent. of all cretins are deaf mutes in greater or lesser degree."[20] The cardiac involvement, which also occurs in the sporadic form, is also common. Goiter is present in a much higher percentage of cases. Many explanations of the cause of cretinic degeneration have appeared: hereditary, chemical through the water supply, geological, bacterial. McCarrison has presented much evidence in favor of the bacterial theory. His experiments and observations over a long period of time included animal experimentation and clinical experience. He says[20]:

> "No better illustration of the action of the toxic product of bacteria could be afforded than that which occurs in experimentally produced congenital goiter, congenital parathyroid disease and cretinism, as a result of administering cultures of fecal organisms to pregnant animals. In this observation the cultures were not killed, but there can be little question that the effects on the fetal organ were due to toxins and not to the direct action of the organisms themselves."

system, which tends to be the seat of a premature arteriosclerosis."

Léopold-Lévi[22] stresses the pluriglandular nature of myxedema and states that while thyroid insufficiency is the predominating factor it is not the only one, and of itself will not account for the complete syndrome.

> "Among the endocrine organs alone, roles of varying importance are played by the hypophysis, the thymus, the testicles and ovaries, as well as by the pancreas, liver, etc. Derangement of these organs reacts upon the tone of the nervous system and the great sympathetic, as well as upon the constitution of the blood plasma. A portion of the symptomatology depends upon disturbance of these various glands. Briefly put, true myxedema is a pluriglandular syndrome, the predominating feature of which is thyroid insufficiency."

Symptoms of Myxedema

The dwarfism characteristic of cretinism does not, of course, exist if the condition has developed after the normal growth process has been completed. The mental symptoms, however, are almost constantly present and may be pronounced in character. There is a characteristic apathy, dullness and disinclination for work. Normal interests are lost and there is a general slowing of thought processes. In many cases more marked symptoms, such as hallucinations and illusions may appear. The weight usually increases. The skin and mucous membranes are severely affected and surface temperature is low, as a result of the lowered metabolism. The lips, nose and cheeks have a puffed, distorted appearance. The infiltrated areas occur all over the body, although especial sites of predilection have been described — cheeks, lids, extensor surfaces, ankles, feet, supraclavicular fossae. The infiltration occurs in the mucous membranes as well as the skin and may extend to the viscera. The skin appears grayish or waxy white, and is infiltrated and furrowed. The hair is dry and brittle, with a tendency to fall out. In the case of the eyebrows, there is a tendency towards thinning of the outer third (Hertoghe's sign). The nails are dry and tend to split easily; the fingers are clubbed and spade shaped. The gums are swollen. The mucosa of the throat and glottis may be affected sufficiently to cause marked changes in the voice. The cardiac muscle is frequently affected, with resulting slowed circulation, and periods of cardiac pain. The vascular endothelium is affected and arteriosclerosis is usual (see Falta, above).

Minor Hypothyroidism

It has been generally recognized by all and specifically mentioned by many of the investigators in thyroid disease that the grave, well marked types (cretinism, myxedema) of hypothyroidism form a very small percentage of the total number of cases found in any locality. The great majority are those cases in which the hypothyroidism is one of lesser degree and in which many of the grosser signs and symptoms — dwarfism, idiocy, etc. — are not in evidence.

"Besides the grave form of thyroid insufficiency, of which myxedema is a maximum expression, there is a lesser thyroid insufficiency. It is of considerable importance inasmuch as, in contradistinction to myxedema, it is very frequent."[23]

Janney[24] states that in its latent form hypothyroidism is of far more frequent occurrence than is generally believed. In a series of cases investigated by him, he found that two-thirds showed definite hypothyroidism, although only three had been diagnosed. Janney notes, as have others, that the greatest diversity of symptoms, seemingly unrelated and not explicable except by means of endocrine pathology, are encountered in hypothyroidism. The action of the thyroid in affecting the metabolism of all types of cells explains the diversity of symptoms arising as a result of its diminution or withdrawal. Léopold-Lévi accounts in part for the diversity of symptoms as a result of the mediation of the sympathetic nervous system.

"In view of the influence of the thyroid gland upon the nervous system, especially the vegetative system, and upon the humoral conditions, it is readily conceivable that insufficiency of the glandular function is attended by an extremely diverse symptomatology, the expression of which is determined, in the first instance, by local predisposition, whether inherited or acquired. The syndrome includes disturbances in varying degree of all the organs the function of which is subordinated to the sympathetic system; which is in its turn dependent upon the activity of the thyroid gland."

An ever larger influence in the causation of a diversity of symptoms is given to an inherent predisposition in some tissues to react to the thyroid insufficiency.

"It sometimes happens that accentuation of a local predisposition leads to the development of an extra-thyroidic syndrome, a morbid complex which in some cases may fitly be termed a malady, of which thyroid insufficiency is the underlying cause. For example: thyroid insufficiency is accompanied by muscular fatigue, partial neurasthenia, an ichthyotic condition of the skin, and alopecia. Now the degree of neurasthenia, myasthenia, ichthyosis, diffuse alopecia, may far exceed that which characterizes the symptoms of thyroid insufficiency, yet these signs may be due to thyroid insufficiency and in that case will respond to thyroid treatment."

Signs and Symptoms of Hypothyroidism

Most of the symptoms described under cretinism and myxedema may occur in minor degree, but seldom are all, and frequently not even a considerable number, present in the same case. If the condition has existed since childhood, the individual will probably be small, poorly developed physically and of low vitality. The signs and symptoms of hypothyroidism in children particularly common are: constipation, partially closed fontanelles, mental dullness and lack of normal incentive and application in play, delayed dentition and re-

tained and irregular teeth, deficient muscular development and disinclination for physical effort, enlarged tonsils, adenoids, impairment of hearing, pasty infiltrated skin, puffy cheeks, thick lips, scanty, dry, brittle hair, thinning of the hair on the outer third of the eyebrows, enuresis. The mentality shows all grades of defect from the idiocy of the cretin to stupidity or "backwardness." These conditions may be evident in school work or be strikingly shown by various mentality tests. General nervousness and irritability is a common symptom. Due to deficient muscular movements of the bowel, constipation is very common in hypothyroidism, although there is also associated deficient excretion of the digestive ferments, gastric and intestinal juice, and bile, which contributes to this condition. There is a tendency to large accumulations in the colon and the intoxication resulting may give rise to symptoms which are the most prominent in the clinical picture. The condition results in a vicious circuit, for the toxemia resulting adds additional work upon the thyroid and depresses it, so that it becomes less and less efficient in correcting the intestinal condition.

In adults the symptomatology is one of general debility and lowered vitality. There is general asthenia, disinclination for physical work and inability for concentration or mental activity. Listlessness and lack of interest are characteristic. The mental symptoms are fairly constant and in advanced cases may result in definite psychoses. The temperature is subnormal and basal metabolism depressed. In marked cases this decrease is constant. Magnus Levy was the first to demonstrate this fact (1895), reporting a reduction of 58 per cent. in myxedema. This is readily conceivable when we remember the great importance of the thyroid effect in stimulating metabolism, and determination of the basal rate by the convenient apparatus now available has become an important aid in diagnosing borderline cases. The assimilation limits for glucose are raised as a result of the deficient thyroid hormone, which is essential to a normal carbohydrate metabolism. As a result of the lowered metabolism and temperature there arise the subjective symptoms of chilliness, cold extremities, etc. Joint symptoms resembling chronic rheumatism have been described (Kocher). Léopold-Lévi and de Rothschild have used thyroid therapy in such cases with constant success, although Falta cautions that this does not necessarily point to a thyrogenic origin of these conditions but may be the result of the beneficial effects of thyroid medication on general metabolism. The muscles are, however, definitely affected and become fatty, and fatigue products accumulate, giving rise to asthenia and muscular weakness. In males, impotence, and in females amenorrhea, menorrhagia and sterility are common.

The involvement of other glands described as occurring as a part of myxedema may also be present in the various grades of milder insufficiency.

> "Other symptoms are frequently associated with those of thyroid insufficiency and certain among these depend for their manifestations upon the derangement of other ductless glands. The important are these:

"1. The symptoms in question are not necessarily associated with thyroid insufficiency.
"2. They may form part of the clinical complex, not of subthyroidism but of hyperthyroidism.
"3. They are associated with lesions or derangements of other endocrinic glands, and these lesions or derangements are capable, on their side, of primary or secondary reaction upon the thyroid body, giving rise either to thyroid insufficiency or to secondary thyroid instability."[22]

Certainly it would appear that the association of other glands, either as a result of thyroid disturbance or preceding it, is as a rule not sufficiently considered either in diagnosis or treatment. Thyroid therapy alone, or thyroid administration for purposes of diagnosis, may be unavailing and lead to no conclusive results through neglect of this point. The hypophysis and gonads which are commonly associated in endocrine disease are frequently involved in a syndrome in which the major symptoms are those of hypothyroidism. Likewise the low blood pressure and asthenia, described above as characteristic of hypoadrenia, may be conspicuous in hypothyroidism and point to an associated suprarenal involvement.

General Consideration of the Signs and Symptoms of Hypothyroidism

1. Infiltration

Infiltration is perhaps the most characteristic sign of hypothyroidism and in advanced cases gives rise to changes in practically all tissues. The pathology of many diverse signs in hypothyroidism, therefore, is the same — thickened lips, lids, skin, mucous membranes, etc. The condition is most marked in the skin and mucous membranes but may extend to practically all of the viscera. The peculiar substance which infiltrates these tissues is of unknown chemical constitution and described as mucoid. It infiltrates the connective tissue of the skin layers and muscle tissue of various organs. There is no pitting on pressure such as is seen in true edema. In minor hypothyroidism Léopold-Lévi describes a transitory infiltration appearing for brief periods and even for part of a day.

"A white indolent edema, which does not pit on pressure, makes its appearance in the vicinity of the eyelids, the forehead and the cheeks; occasionally there is transitory swelling of the feet, and the subject finds that his boots are temporarily too tight for him. Or the fingers may become sufficiently swollen to render the removal of the rings a matter of difficulty."

Léopold-Lévi's description of this type serves to emphasize the fact that even in marked hypothyroidism the infiltrated material may vary from time to time and in some cases may even disappear.

2. Mental and Nervous Symptoms

Symptoms referable to the nervous system and defective mental development are of constant occurrence. In congenital cretinism and marked hypothyroidism in the young, definite structural change in the brain and central nervous axis are present. The normal

"*Vagotonic Hypoadrenia.* A young lawyer was referred last winter by Dr. Wilmer, to whom he had been sent because of distress during prolonged use of the eyes. There were no physical abnormalities sufficient to account for this, so Dr. Wilmer referred the patient to me for neurological survey, partly because of an apprehensiveness which the patient had developed as a boy and because of an increasing lack of stamina, indigestion and paresthesiae. Examination showed a low blood pressure, 110 and 72, decreasing on standing, the following day falling to 90 and 62, increasing to 102 on standing. Pulse 102; positive Ascher phenomenon, positive Trousseau sign, Chvostek sign however absent, and history of tetanic cramp and paresthesiae in the legs after prolonged sitting. The reaction to pilocarpine was excessive, there being chills, nausea, weakness, and urethral dragging pain. Treatment of the hypoadrenia alone by adrenal substance caused considerable improvement. This was later augmented by small doses of thyroid, pituitary, and gonads, when great improvement followed."

In asthenia with marked suboxidation and lowered metabolism and evidence of general hypothyroidism, the addition of thyroid may be exceedingly valuable. The general results of thyroid therapy are among the most striking observed in medicine and in definitely diagnosed, uncomplicated hypothyroidism the administration of thyroid extract alone may be sufficient. In cretinism and myxedema the improvement in the mentality and physical symptomatology may result in a return to a close approximation to normal. This improvement is usually prompt, a few days sufficing to bring an easily discernible change. The dosage is from 1 to as much as 5 grains daily, the greater number of cases requiring low dosage — from 1 to 2 grains daily. In minor hypothyroidism the effects are most gratifying and low dosage is advisable.

It will be noted that in "general debility" with asthenia, suboxidation, low blood pressure, mental and physical lassitude, lack of "drive," etc., as the cardinal symptoms, there is usually defect of cell metabolism itself. In hypoadrenia and in hypothyroidism there is accumulation of the catabolic products, fatigue substances, and (in hypothyroidism) definite infiltration of the tissues of the body. The effect of Hormotone is one of stimulation of the entire group of glands described by Falta as the acceleratory or dissimilatory, and is attended by stimulation of the lowered metabolic processes, increase in respiratory quotient, stimulation of the tissues innervated by the sympathetic, correction of suboxidation and the resulting accumulation of fatigue substances, and increase in adrenal function, which has been shown to be so essential in the maintenance of muscle efficiency and the prevention of fatigue and asthenia.

The frequent association of functional disturbances of the thyroid, hypophysis, suprarenals and gonads, with the resulting clinical picture that is not characteristic of pure type disturbance of any single gland, has been described. These complex involvements account for the great

majority of the cases of general debility and "run-down" conditions, which certainly form one of the most numerous groups met with in general practice. In the treatment of these cases it is unnecessary to relate the insufficiency of the usual "tonic" drugs or to note the fact that the endocrine substances used in medicine are the only ones which definitely raise lowered basal metabolism. The advisability and even necessity of combined therapy has been shown.

> "Where thyroid insufficiency is associated with other endocrine insufficiencies, the glandular therapy should be equally complex; ovarian, testicular, suprarenal and pituitary extracts may all be employed with advantage in suitable cases." (Léopold-Lévi.)

Summary of Treatment

In simple asthenia, without disproportionate involvement of any particular gland, Hormotone, in a dosage of 1 or 2 tablets three times daily.

In cases of determinable involvement of the suprarenals — hypoadrenia — in which the adrenal factor is predominant, Hormotone in a dosage of 1 or 2 tablets three times daily, supplemented with 1 tablet (2 or 5 gr.) of Entire Suprarenal Substance.

In cases with involvement of the thyroid, 1 or 2 Hormotone Tablets three times daily, supplemented with 1 tablet (1/10 to 1½ grs.) of Thyroid Substance, the thyroid dosage depending upon the extent of the symptoms of hypothyroidism.

SENILITY

The similarity in general appearance of cases of well marked hypothyroidism and senility has frequently been noted, in both the psychic and physical features of the two conditions. The characteristic mentality of the aged, with its loss of memory, tendency to somnolence and lack of grasp of difficult or complex matter, has its counterpart in the mentality of marked hypothyroidism. The impaired hearing, dry and scanty hair, lowered or lost sex function, and arteriosclerosis, of the one are likewise characteristic of the other. Horsley, in particular, and others following him, noted the increase in connective tissue and the alteration in the skin as common to both conditions.

Senile Changes Pluriglandular in Origin

In senility, however, and particularly in premature senility, considerations of clinical observation, as well as the physiological correlation of the endocrine glands, warrant the belief that premature senility is not due to subfunction of the thyroid alone, diverse and widespread as these effects are.

> "For reasons less obvious and in a manner less dramatic than the menopause, the conditions surrounding the mere advance of years tend to produce inadequacy of the thyroid function. It is not that the thyroid gland declines more rapidly than the other internal secretory glands, for all of them, even including the spleen, tend to diminish both in size and activity as the years advance. It is that the thyroid gland is so important to the economy that any diminution in its activities reflects itself unmistakably in a great many directions."[26]

Certain symptoms and signs indicate the involvement of other endocrine tissues and the condition of senility very probably arises as a result of a gradual pluriglandular hypofunction. "Besides the thyroid there are also different other ductless glands whose degeneration produces old age. These are the sexual glands, the pituitary body and the adrenals."[27] Falta is in accord with this opinion in so far as it is applied to premature senility. He says:

> "In a detailed study Lorand has upheld the idea that the degeneration of the ductless glandular system is chiefly the cause of senility. I would not concur with this, so far as physiological old age is concerned, but believe much more, as does also Ewald, that the ductless glandular system like every other organ participates in the involution of old age. There is on the other hand a pathological old age, setting in prematurely or associated with distinct accentuation of the cachexia. The premature senility which develops in most of the diseases due to giving out of function, and especially in multiple ductless glandular sclerosis, makes intelligible to me the fact that degeneration in the ductless glandular system may be one of the causes of pathological age."[21]

Autointoxication

The conception of autointoxication as a contributing factor in old age has also been brought into relation with pluriglandular endocrine involvement by many authors and such intoxication seems to follow as a necessary part of the glandular disturbance. Both the adrenals and thyroid, which play an important part in the antitoxic mechanism of the body, fail to exert their normal antitoxic action and the widespread systemic effects of the intestinal toxins proceed unhindered.

> "In true senescence, normal decline, the outstanding phenomena have to do with degeneration of the ductless glands. Since these glands regulate the effects of self poisoning, when they fail of their integrity, autointoxication progresses almost unhindered."[28]

The effects of adrenal insufficiency in establishing a premature senility have been noted and these effects may be found in the diverse symptomatology of senility. Sajous assigns an important place to the adrenals in this condition.

> "In the light of the data I have submitted, however, it is clear that the lesions to which the adrenals are subjected during infection and autointoxication, from birth to the last day of life, do greatly shorten it by limiting the functional area of the organs through the fibrosis they entail. It is quite probable, in fact, that centenarians owe their prolonged longevity mainly to integrity of their adrenals."[16]

Emotional Factors

The effects of prolonged and intense emotional and psychic activity have been stated to contribute to premature senility by many physicians and the idea is current among the laity as well. If the reservation is made that a moderate normal mental activity is necessary to the prolongation of life, the im-

portance of excessive emotional and psychic activity in causing senile changes will probably be doubted by none. Taylor says:

> "Conditions of fierce, frantic competition, breeding as they do envy, hatred and malice; inviting to indiscretions in act, in amusements, in food, in drink, irregularity in hours of sleep, inadequate forms and kinds of rest and exercise, form the foundation of and supply favorable conditions for presenility. Hence it comes to pass that when these unfortunates reach early middle age they show the earmarks of overcombustion, disintegration, cellular decline."[28]

Having important bearing upon the mechanism of these emotional states would appear to be the work of Cannon, who demonstrated the effects of the strong emotions, fear, rage, etc., in causing a great increase in adrenal activity and epiriephrin output. It seems probable that an individual whose mental life has been filled with a succession of such states develops an early functional incapacity of the adrenals and a consequent early appearance of the signs of senility.

Influence of the Sex Glands

The influence of the sex glands in maintaining physical and mental vigor has long been known and the development of signs and symptoms of senility following castration is of constant occurrence. This relationship has within the last few years been emphasized by the experiments of Steinach, both by transplanting sex glands and by effecting a stimulus to the individual male gonad by vasectomy. In these experiments upon old and decrepit animals (male and female) the transplantation of ovaries and testes made the most remarkable change in the animal. Animals previously feeble, decrepit and unfit for breeding purposes gained in physical vigor and appearance, and became sexually potent. In commenting upon these experiments Lorand says:

> "It is interesting to note that at the autopsy of these rejuvenated old rats the sexual organs, including the ovaries, mammary glands, and uterus, were found in the same condition as would have been expected in young rats.
>
> "Thus, upon transplantation of the ovaries of young rats into old ones, the new ovaries made up for the lost functions of the former ovaries which had undergone degeneration by reason of advanced age. Along with this came the remarkable transformation into a young animal, with all the attributes of a young female, again proving the truth of what the great Belgian physician, Jean Batiste Helmont, said several centuries ago, *viz.*, that a woman is made what she is by her ovaries."[27]

The gonad influence on the organism is very marked and in young adult life affects not only the physical but the mental development as well.

> "Nearly all the great men of present and past times, including great writers, artists, famous generals, etc., have had highly developed sexual proclivities. Their high grade intellect offers an enormous contrast to the inferior mental qualities and feeble intellect of castrates."[27]

The onset and development of the condition of premature senility seems to be intimately connected with the endocrine glands, even such factors as autointoxication, emotional strain, etc., acting through them. Various observers have placed emphasis upon this or that gland, all, however, recognizing the pluriglandular nature of the process. The thyroid and gonads appear to be central figures in the causation, although it is by no means believed that they are the only ones. The thyroid element has been discussed and is of such a nature that premature senility has been likened to hypothyroidism. The influence of the thyroid upon all tissues of the body makes its importance in this connection easily understood. The influence of the gonads is scarcely less striking, and the experimental work has served to emphasize the function of this tissue in maintaining and restoring the vital processes characteristic of youth. The part of the adrenals, while not so strikingly apparent as the thyroid and gonads, seems to be important. Premature senility, then, is a condition the establishment of which involves a definite group of glands and is not wholly dependent upon any one of them.

TREATMENT

The effects of organotherapy in bringing about an amelioration of the symptoms, and as a preventive measure in delaying their appearance, has been thoroughly demonstrated. The correction of vicious modes of living and habits is of prime importance and excessive indulgence in food, alcohol, tobacco, work and stimulants of any kind should be avoided in any treatment looking toward the rejuvenation of the individual. Organotherapy should be used in conjunction and the prognosis is most favorable.

> "Old age being caused by degeneration of the endocrine glands, especially the thyroid and sexual glands, all that is necessary to secure rejuvenation is to improve the condition of these glands. The best and easiest way to do this is to administer by the mouth extracts of these glands, after their extirpation from healthy animals. As long as thirty or more years ago it was proved that when one of these glands, such as the thyroid, is degenerated, all of the normal functions of this gland can be reproduced by ingesting extracts of the thyroid of sheep. The diseased gland is thus successfully replaced by the ingestion of the animal gland.
>
> "To bring about rejuvenation I have given to old men and women, and also to persons suffering from premature old age, extracts of the thyroid and sexual glands of animals. As already mentioned, marked success attended the procedure. The persons treated looked considerably younger after it, to the extent of ten or fifteen years and sometimes even more. The wrinkles in the face already began to disappear four or five weeks after the treatment, and at the same time previously corpulent persons, losing their excess of fat, were made to look slender, thus imparting a youthful impression."[27]

In a discussion of the neurotic and neurasthenic conditions arising in elderly women Leonard Williams says:

> "Of polyglandular therapy I have not had very much experience, but since I have been using a mitrailleuse called Hormotone I have had considerable success in those cases just referred to as benefited by pituitary."[29]

Hormotone in a dosage of 1 or 2 tablets t. i. d. is usually sufficient and the effects in restoring physical and mental vigor are most encouraging. The added strength and sense of well-being and the maintenance of the physical and mental vigor are not only satisfying to the individual himself but are of interest and value to society as well, for at a time when the maximum of intellectual efficiency, through education and years of experience, has been reached, the retrograde changes of senility ordinarily remove in large measure the productive and creative capacity and the value of the individual is lost to society. Any system of treatment, therefore, which will add, by rejuvenation effects, any considerable period of vigor and usefulness to the period of life in which the highest attainment is possible, is of more than ordinary interest to the physician and to society.

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PART IV

CHAPTER I

GROWTH

The internal secretions are fundamentally concerned in the growth process of the organism. Growth is one of the elemental characteristics of living tissue and, as it is easily measurable, has been the subject of much investigation by endocrinologists, in so far as it is affected by the internal secretions. Growth, however, is an exceedingly complex process, due to many factors other than internal secretions, and failure to take into account these other factors has resulted in much confusion, especially in feeding experiments conducted to ascertain the effects of particular endocrine glands. Essential factors, such as temperature, food, the accessory food factors (vitamines), etc., need not be discussed here. In animal experimentation they must be carefully taken into account. The possible relationship of the vitamines to the hormones may be briefly referred to. Their identity has been asserted by some, and there seem to be many points of similarity in their effects in physiology and growth and the manner of producing these effects. Vitamines are indispensable for growth, continued reproduction and well being. They must be reckoned with in all considerations of diet. Like hormones, they produce their effects in the most minute quantities, and it has been inferred from this that they act as catalysts. Robertson [1] is not of this opinion, however, but suggests that the vitamines may be used in the building of hormones by the body. Vitamines themselves are apparently only synthesized by plants and the animal organism is unable to produce them from simpler materials. Robertson says of them:

Relation of Vitamines to Hormones

> "Little doubt can be entertained that the accessory foodstuffs actually enter into the manufacture of substances produced by tissues, whether these are structural elements of protoplasm, or substances elaborated by them (for example, enzymes) in the performance of their functions, or substances elaborated by a relatively small mass of specialized tissues for the advantage of the whole organism (for example, hormones). Having regard to the extremely small quantities of certain hormones which suffice to achieve their characteristic effects, the latter supposition will appear to many the most probable."

The Ovum Contains the Embryo in the Rough.

The endogenous growth factors include the influence of the several internal secretions, the innate species limitations, and the growth periods. The normal limitation of growth of an individual to an approximation of the norm for the species is self evident. Development, as well as growth, is influenced by the internal secretions. The tendency to definite tissue differentiation, organ formation and the progress

to completion of the norm type of the species probably exist as a result of the physical constitution of the cytoplasm of the ovum.

> "The facts of experimental embryology strongly indicate the possibility that the cytoplasm of the egg is the future embryo (in the rough) and that the Mendelian factors only impress the individual (and variety) characters upon this rough block. * * * In any case, to-day we can state that the cytoplasm contains the rough preformation of the future embryo."[2]

As the ovum develops into the embryo there is evident an anlage or specific groundwork for each organ and structure. The factors determining the formation of these anlagen are, as stated by Loeb, unknown. Their existence he shows by several interesting references to experimental biology. Thus from the anlage of a foreleg only a foreleg will develop, and, irrespective of the part of the body to which this anlage is transplanted, even if this be the point from which hind legs usually arise, only a foreleg will develop. This is also true for the anlage of the eye.

Now the great function of the internal secretions in growth and development seems to be that of a stimulator; something which supplies the impetus to action of a latent mechanism. Loeb points out that some of the earlier botanists, J. Sachs in particular, had offered as an explanation of general correlation of parts and the formation of organs, the presence of specific substances circulating in the sap. "Such substances are known now under the name of 'internal secretions' or 'hormones.'"[3] Of the results of thyroid feeding, of transplantation experiments and other experimental work, Loeb[4] says:

Growth and Development under Hormone Control

> "These and other observations of a similar character leave no doubt that substances circulating in the blood and not the central nervous system are responsible for the phenomena of growth and metamorphosis."

Growth and development are, therefore, from the very moment of fertilization of the ovum, subject to internal secretion control. Internal secretions are the directing agents which determine the growth and characteristics of the latent anlagen or preformed groundwork in the ovum of the future embryo and individual. They are, therefore, not only of interest in the growth and development of the individual, but they are part of the mechanism of heredity. Loeb,[5] in a discussion of the mechanism of Mendelian heredity, states this as follows:

> "Is the organism nothing but a mosaic of hereditary characters determined essentially by definite elements located in the chromosomes; and, if this be true, what makes a harmonious whole organism out of this kaleidoscopic assortment? * * * How can a factor contained in the chromosome determine a hereditary character of the organism? To the first question we venture to offer the answer which has been already suggested in various chapters of this book, that the cytoplasm of the egg is the future embryo in the rough; and that the factors of heredity in the sperm only act by impressing the details upon the rough block. This

metaphor will receive a more definite meaning by the answer to the second question. The characters which follow Mendelian heredity are morphological features, as well as instincts. For the former we have already had occasion to show in previous chapters to what extent they depend upon the internal secretions or the existence of specific compounds in the circulation, and the same is true for the instincts. This then leads us to the suggestion that these determiners contained in the chromosomes give rise each to the formation of one or more specific substances which influence various parts of the body."

This rôle of the internal secretions in development seems largely to accelerate a pre-existing tendency to action. Whether, as may be inquired, they contribute any qualitative elements can not be answered positively. Of the action of thyroid, perhaps the best studied of all, Uhlenhuth says:[2]

"Little is known as to the mode of action of the internal secretions, although we do know, through the discoveries of Kendall, that the thyroid hormone acts as a catalyser and augments the metabolic process in an effective and specific manner. If this be the only peculiarity of the thyroid hormone, by means of which it produces new structures, it may mean that mere quantitative differences are perceived by our sense organs as qualitatively different morphological structures. This view fits in well with observations of Child on diverse groups of organisms. According to this author, the qualitative differentiations along the various axes of an organism are simply the expression of quantitative differences of metabolism. For instance, the formation of the head, according to Child, takes place wherever in an organized living system a metabolic maximum is formed."

Growth Periods

The influence of growth periods has until recently not received general recognition. Robertson has recognized the influence of age as a factor, and describes three main cycles of growth, each cycle made up of a phase of slow growth followed by a period of rapid growth, again succeeded by a period of slow growth. The first part, or the period of increasing growth, he calls the "autokinetic phase," and the latter part or period of decreasing growth the "autostatic phase." He describes these cycles of growth thus:[1]

"The growth of man, therefore, consists of periods of rapid and slow growth which alternate with one another, so that if we plot the growth in any dimension, for instance weight, on 'coordinate paper,' measuring weights vertically and ages horizontally, we obtain a diagrammatic picture of the growth-process which is not a straight line, nor even a single curvilinear sweep, like the outline of a parabola, or of the logarithmic curve which represents the progress of the ordinary type of chemical reaction. On the contrary, our diagram reveals distinct waves, or large oscillations in the growth-process, and resembles, as a matter of fact, the

diagram which may be obtained by superimposing three S-shaped curves upon one another in such a manner that their adjacent extremities merge into one another."

Biedl [4] describes these periods as follows:

"Periods of growth have been recognized by all who have investigated the question. The first growth period includes the first five or seven years of life, and the second period is that just before puberty. When I review the results of a series of experiments in pituitary feeding I carried out some years ago, I perceive a marked decline of response between the seventh and thirteenth years, an abundant activity during puberty, and a similar activity during the period of infantile growth. Therefore, I conclude that all experiments with growth activating substances must take account of these sensitized and unsensitized periods."

Robertson's periods appear generally to coincide with these. He outlines them as follows:

1. From the ovum to about one year after birth.
2. From the end of the first year to the maximum at 5½ years, and then falling off.
3. From the end of the second period, reaching the maximum at puberty and ending at adult life.

In animal experiments the normal growth curve for the kind of animal used must be ascertained. This has been done for some of the commonly used experimental animals. The period of greatest growth is the intrauterine period, and after birth the rate of growth progressively though not uniformly diminishes. The metabolism of the highly complex higher vertebrates is active and the elimination of wastes and the thorough oxidation of intermediate products are not entirely adequate. Throughout life, therefore, the tendency to tissue death is always present, and progressively increases. The marked effect of the internal secretions in maintaining normal metabolism suggests another and indirect manner of promoting growth through their effects on general metabolism. The action of the internal secretions in stimulating or regulating growth is due to special substances described by Gley [5] as harmozones or morphogenetic substances. The endocrine organs giving rise to this class of substances are the thyroid, pituitary, adrenal cortex, gonads and pineal. A full discussion of the evidence of growth regulation will be found under the section devoted to endocrine organs themselves. Only a generalization will be given here. Before describing these endocrine tissues, however, mention will be made of certain trophic substances, indispensable to growth, named by Carrel, trephones.

Trephones In experiments upon the growth of epithelial and connective tissue in culture media outside the body, it was ascertained that these tissues do not utilize, from blood serum surrounding them, the materials for the synthesis of protoplasm. Growth is, therefore, impossible. When, however, certain substances contained in the juice of embryonic tissues or in the cell-bodies of lymphocytes are added to such a culture, growth and cell proliferation proceed rapidly. These substances,

the trephones, differ fundamentally from hormones in the fact that they are nutrient, nitrogenous substances used up in the formation of new protoplasm, whereas the hormone is a catalyst and accelerates metabolism without itself being used as a material.

In the experiments in the cultivation of fibroblasts *in vitro* this tissue proliferates as rapidly in saline solution as in serum, but does not increase in volume in either, from which it may be concluded that the nitrogenous elements of plasma and serum are not available as food elements in building protoplasm of connective and epithelial tissue. Apparently, the only nitrogenous compounds which can be utilized are the trephones, the addition of which in the form of embryonic tissue juice causes a rapid growth and proliferation. These substances have also been proved experimentally to be present in the leukocytes which secrete them *in vivo*, as well as *in vitro*. This has been demonstrated by the proliferative effects produced by extracts from inflamed adult connective tissue. Leukocytes appear to possess the property of synthesizing these trephones or nitrogenous nutritive compounds from the nitrogen compounds of the serum and, therefore, play a fundamental part in nutrition. Carrel summarizes this as follows:[7]

> "Lymphocytes appear to be endowed with a function of primary importance in the nutrition of tissues. As is well known, fibroblasts and epithelial cells do not synthesize protoplasm from serum constituents, but are capable of obtaining from embryonic tissue juice certain substances which determine unlimited proliferation. Leukocytes which, like embryonic cells, contain growth-promoting substances have the power to supply connective and epithelial tissues with the principles necessary for growth. The food material used by lymphocytes in the manufacture of the essentials which determine the multiplication of fibroblasts or epithelial cells comes from blood serum. Thus, lymphocytes and macrophages can be considered as mobile unicellular glands which transform some of the serum constituents into trephones and set them free in blood plasma or interstitial lymph as a food for fixed cells. They play the rôle of trephocytes, or nursing cells, for epithelium and connective tissue. As trephones are also present in the aqueous extracts of glandular and other tissues, it is permissible to suppose that endocrine glands, like leukocytes, may secrete nutrient substances for certain tissues, and not only hormones."

Trephones, however, are not the only substances elaborated by leukocytes and disintegrating leukocytes liberate a variety of substances. The trephones explain many of the facts in connection with tissue repair in adult tissue. The irritant incident to trauma brings leukocytes to the site (inflammation) which liberates the trephones necessary for rapid cell proliferation and upbuilding of new tissue, which could not be synthesized from the serum in any other way than by utilizing the nutrient trephones

> "Our experiments indicate that lymphocytes remain through life as a store of embryonic growth-promoting substances or trephones, which may cause a resumption of cell activity when it is needed."[8]

Trephones are not present in older animals in the same quantity as in younger, although other factors affect the growth-promoting power of serum. The trephones are also probably elaborated by the endocrine glands in addition to the hormones.

> "The presence, in embryonic tissue juices and in glandular and leukocytic extracts from adult animals, of principles increasing the rate of multiplication of fibroblasts and epithelial cells suggested the possibility that these substances are secreted by leukocytes and endocrine glands."[6]

The differences between the hormone and the trephone have been referred to. Both seem to be required for growth.

Thyroid

The thyroid exerts a marked influence on the growth of the organism, and the stunted growth of the cretin is familiar to all. The manner in which these effects are produced is unknown. The demonstrated catalytic effect of the thyroid internal secretion in increasing metabolism may account for it as an increased utilization of the food elements in which anabolism exceeds catabolism. The thyroid affects growth in animals, high or low in the animal scale. The metamorphosis of tadpoles, first shown by Gudernatsch, is hastened by thyroid feeding and the growth of cretins is remarkably stimulated by the same procedure. In thyroidectomized animals growth is greatly retarded or ceases. Thyroid feeding in animals results in increased growth, if the quantity administered is small enough to raise metabolism to a point at which catabolism does not exceed anabolism (see page 48). In lower forms there is some evidence that inorganic iodin is effective in growth promotion and metamorphosis. There are several explanations for this. In higher forms, however, the thyroid secretion is indispensable and iodin administration can not replace thyroid substance in feeding experiments in thyroidectomized animals. Animal experiments and clinical pathology, therefore, have firmly established the growth promotion of the thyroid internal secretion.

Pituitary

Animal experiments and clinical pathology have demonstrated the influence of the anterior pituitary in growth almost as certainly as that of the thyroid. Uhlenhuth states:[8]

> "On the basis of our present knowledge it seems safe to say that the hypophysis elaborates a specific substance, which in some way as yet not well understood accelerates growth, development of the sexual characters and, in certain groups of organisms, bodily development in general."

This conclusion is borne out by an analysis of the results of animal feeding and by the evidence from clinical medicine, such as the growth disturbance in Fröhlich's dystrophy, acromegaly, etc.

GONADS

The effects of the gonads on both growth and development are well defined, constant and in many respects the most striking of all the endocrine tissues. Internal secretion determines the whole structure and configuration peculiar to sex. All the secondary sex characteristics in higher forms of animals are determined through this agency. The following is taken from Weil:[7]

> "In our further study we will adopt the views of Tandler and Gross, which, as well as those of others, are supported by the experiments of Steinach, that the secondary sex characteristics, *i. e.*, all the distinctive differences between the sexes, with the exception of the genital glands (testis and ovary), were originally 'systemic characteristics,' which owe their evolution and development solely to the 'harmonious cooperation of the endocrine glands,' that, therefore, the somatic cells taken altogether were originally an 'asexual embryonal form' (Lipschütz), which first acquires the sex property through the action of the internal secretions."

Sex itself is determined by heredity, a fact now well established in biology and stated by Howell as follows:[8]

> "We owe the establishment of this important generalization largely to American investigators (McClure, Wilson, Stevens). It enables us to treat sex as a Mendelian characteristic transmitted by certain hereditary units or determiners."

In higher animal life this is limited to determining whether an organism shall develop a male or female interstitial gland. The growth and development thereafter of all the conspicuous secondary sex characteristics and the sex gland itself are controlled by the internal secretion of the interstitial gland. This is well described by Biedl[9] for the male individual as follows:

> "We are led to the inevitable conclusion that the hormone which gives to the organism its male characteristics is elaborated in the cells of Leydig in the interstitial tissue. In spite of their mesodermal origin, these cells are able actively to produce certain specific substances and to transfer these substances to the blood stream; such being the case, we are justified in describing them in their totality as an interstitial gland.
>
> "It is highly probable that by the agency of its secretory products this gland is responsible for the development of the male sexual gland from the primitive genital trace. That it has a determining influence upon the normal development and maturity of the generative portion of the sexual gland, upon the formation of the secondary genital organs and upon the existence and persistence of those morphological and biological characteristics which are the property of the male sex is undoubted."

In the female the homologous interstitial cells found in the ovary determine the female characteristics. Although the original determination

of sex is a Mendelian heritable characteristic resident in the determiner of the chromosome, even here the internal secretions may be an essential part of the mechanism, as it is suggested by Loeb that the determiners themselves may give rise to internal secretions which direct the subsequent development of the tissues.

Animal experimentation has furnished striking evidence of the effect of the interstitial tissue of the gonads in growth and development.

Steinach's experiments of grafting ovaries into castrated males showed that the animal was literally transformed into a female, showing all the instincts and structural peculiarities of the female. Transplantation experiments in general have shown that a successfully transplanted gonad in any part of the body carries on its functions in metabolism, growth and in the development of the secondary sex characteristics. Such experiments have clearly demonstrated an internal secretion effect as opposed to a nervous mechanism. Removal of ovaries results in cessation of menstruation; grafting an ovary under the skin re-establishes menstruation. Hermaphroditism may be explained by the occurrence and persistence of the sex glands of both sexes in the same individual.

Suprarenal Glands

The suprarenals, and particularly the suprarenal cortex, appear to have some important function in growth and development, particularly of the sex glands. This is indicated by the hypertrophy during pregnancy, by the hypertrophy of the gonads following suprarenal feeding, by the association of suprarenal cortex hypertrophy and sexual precocity, by hypertrophy of the sex organs with tumors of the cortex, by the association of small cortex and low sexual activity and development, and by the hypertrophy of the cortex following castration.

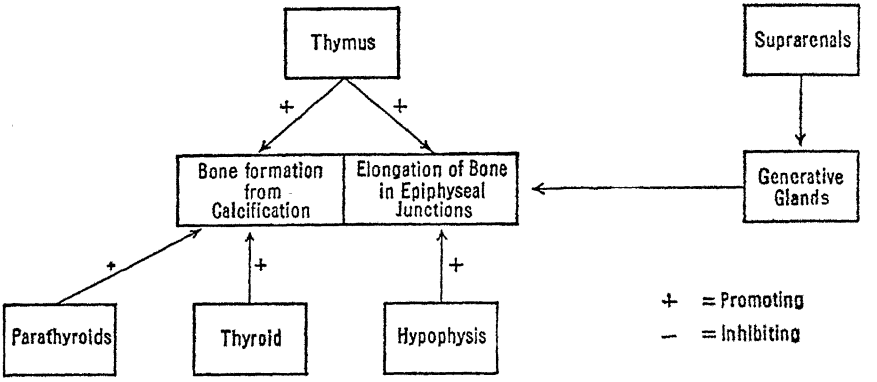
Pineal

The pineal body is believed to have some function in the growth and development of the sex apparatus. Cases of pineal overactivity, resulting from tumors, are attended by increased general bodily growth, increase in mental growth and marked sexual precocity. These latter are perhaps the most characteristic and constant effects, although they may be wanting. Feeding experiments (McCord) also show stimulation of body growth, and in a less evident manner mental and sexual precocity. The therapeutic administration of pineal preparations has been attended by some positive as well as negative results in stimulating physical and mental growth in backward children.

Thymus

The thymus is frequently mentioned as influencing in some manner the growth of the body, and may have some effect upon skeletal growth through an influence upon calcium metabolism. Most observers who have investigated the evidence are inclined to deny any growth controlling effect of the thymus, and some even deny it a place among the internal secretion

organs. Weil,[7] however, accorded it a place in his diagrammatic scheme of the interrelations of the internal secretory organs in the processes of growth and development. The pineal is not represented. The scheme is as follows:



Although undoubtedly the gaps in our knowledge of the relations of the internal secretions to growth are very large, the facts already established rest upon very sure foundations, and the internal secretion factor will undoubtedly be a very large one in explaining the mechanism of this fundamental phenomenon of biology.

Influencing Growth Through Organotherapy

The conspicuous part played by the endocrine system has suggested the use in those conditions of faulty and delayed mental and physical development of those gland substances which have important growth controlling functions. The treatment of that large group of cases described as backward children must take into account that the basic defect in mental or physical development is very largely one of faulty internal secretion. These endocrine defects may be either congenital or acquired. Haverschmidt (inaugural lecture as professor of pediatrics, Utrecht, 1920) states that "the nature of and severity of the disturbances in the vital processes of the child, its appearance, well-being and development, are born with it and often transmitted through heredity. * * * The study of the endocrines is constantly emphasizing the theory that these inferiorities of congenital nature are caused by functional insufficiencies of the endocrines during the development of the fetus. The results of the endocrine activities and insufficiencies bestow upon the child the imprint of endocrine perfection or imperfection, which we call the constitution of the child."

These endocrine defects are manifested by mental and physical abnormality or retardation. These frequently require special educational facilities, as well as medical treatment. Physical stigmata indicative of malfunction of several glands may be frequently found and confirm the diagnosis as to endocrine origin. There are cases (true feeble-mindedness, idiocy with structural defect of the cerebral cortex) which do not fall

within the class in which successful results may reasonably be expected by organotherapy. With the abnormal mental conditions in later life, the thyroid, pituitary, adrenals and gonads are frequently associated,[10] and such cases form a very large part of the practice of physicians devoting their practice to this phase of medicine.

Before treatment by organotherapy, the child should be subjected to a careful mental and physical examination. Many "defective" children are found to suffer from nasopharyngeal disease, errors of refraction, diseased tonsils, impaired hearing, etc. Such conditions should be corrected and may relieve the "deficiency." Organotherapy, once instituted, must be supplemented by the best hygienic conditions. Nutritive food, proper surroundings and adequate special educational training are indispensable to success.

The organotherapeutic treatment is by means of desiccated substances of those glands which are known to have important functions in normal growth—anterior pituitary, pineal, thyroid, suprarenal and ovary (or testis). Clinical experience in the use of such combinations has justified their use and is in accord with the theoretical considerations upon which the treatment is based. Some investigators have reported favorable results from the use of single glands, such as pineal, thyroid, pituitary, etc., but in the great majority of cases the combination of glands is the more effective treatment. Results such as reported by Berkeley are indicative of the value of combined gland therapy.[11]

Pineal Compound No. 3 for males and No. 4 for females offers a satisfactory combination for treatment. One or two tablets three times daily is sufficient dosage, although it is advisable in many cases to increase the dosage somewhat to correspond with the "growth cycles," at which time the patient might reasonably be expected to respond more readily.

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PART V

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	In one bottle
Amylzyme	Powder 1 oz.
	caps. 40
	100
Brain Sub.	Powder 1 oz.
Brain & Spinal	2-gr. tabs. 100
Corpus Luteum	Powder ⅛ oz.
	1 oz.
	2-gr. tabs. 50
	2-gr. *C. C. T. 50
	100
	5-gr. tabs. 50
	100
	5-gr. caps. 50
	100
	1 c. c. ampoules, ½ doz.
Duodenal Sub.	Powder 1 oz.
Epinephrine	Powder 1 grain
	Chloride Sol., 1-1000 1 oz.
	1 c. c. ampoules, 1 : 10,000 ½ doz.
Kidney Sub.	Powder 1 oz.
	2-gr. tabs. 100
	5-gr. caps. 100
Lecithin, Commercial	1 oz. jars
Liver Sub.	Powder 1 oz.
	3-gr. tabs. 100
	5-gr. caps. 100
Lymphatic Gl.	Powder 1 oz.
	3-gr. tabs. 100
Mammary Sub.	Powder 1 oz.
	3-gr. tabs. 100
	5-gr. caps. 100
Marrow—Red	½ pt.
Bone Glycerole	1 pt.
Orchic Sub.	Powder 1 oz.
	2-gr. tabs. 100
	5-gr. caps. 100
Ovarian Sub.	Powder 1 oz.
	1-gr. tabs. 100
	2-gr. tabs. 100
	2-gr. *C. C. T. 100
	5-gr. tabs. 50
	100
	5-gr. caps. 50
	100
Ovary w/o Corpus Lut.	Powder 1 oz.
	5-gr. caps. 100
Ox Gall	Powder 1 oz.
Pancreatin (U. S. P.)	Powder 1 oz.
	2-gr. tabs. 100
	5-gr. caps. 100
Pancreatin, High Test	Powder 1 oz.
	5-gr. caps. 100

* C. C. T. = Chocolate Coated Tablets.

	In one bottle
Pancreatin & Soda	Tablets 100
Parathyroid	Powder ⅛ oz.
	1/20-gr. tabs. 100
Parotid	Powder 1 oz.
Pepsin (U. S. P.)	1 oz.
Pineal Sub.	Powder ⅛ oz.
	1/10-gr. tabs. 100
Pituitary, Entire	Powder ⅛ oz.
	1 oz.
	½-gr. tabs. 50
	100
	1-gr. tabs. 50
	100
	2-gr. tabs. 50
	100
Pituitary, Ant.	Powder ⅛ oz.
	1 oz.
	1-gr. tabs. 50
	100
	2-gr. tabs. 50
	100
Pituitary, Post.	Powder ⅛ oz.
	1/10-gr. tabs. 100
	½-gr. tabs. 100
	(Liquor Hypophysis)
	½ c. c. ampoules, Ob., ½ doz.
	1 c. c. ampoules, Ob., ½ doz.
	1 c. c. ampoules, Surg., ½ doz.
	Extract (Oral) ½ oz.
Placenta Sub.	Powder 1 oz.
	3-gr. tabs. 100
	5-gr. caps. 50
	100
Prostate Sub.	Powder 1 oz.
	2-gr. tabs. 100
	3-gr. caps. 100
Spleen Sub.	Powder 1 oz.
	3-gr. tabs. 100
	5-gr. caps. 100
Suprarenal (U. S. P.)	Powder 1 oz.
	1-gr. tabs. 100
	3-gr. caps. 100
Suprarenal Cortex	Powder ⅛ oz.
	1 oz.
	1-gr. tabs. 50
	100
	2-gr. tabs. 50
	100
	3-gr. caps. 50

	In one bottle
Suprarenal Medulla	Powder 1 oz.
	2-gr. tabs. 100
Thymus Sub.	Powder 1 oz.
	3-gr. tabs. 100
	5-gr. caps. 100
Thyroid (U. S. P.)	Powder 1 oz.
	1/100-gr. tabs. 100
	1/10-gr. tabs. 100
	¼-gr. tabs. 100
	½-gr. tabs. 100
	1-gr. tabs. 100
	2-gr. tabs. 100
	2-gr. *C. C. T. 100
	1-gr. caps. 100
	2-gr. caps. 100
	3-gr. caps. 100
	5-gr. caps. 100
Tonsil	Powder 1 oz.
	3-gr. caps. 100

* C. C. T. = Chocolate Coated Tablets.

Nucleo-Protein Products

Ovarian	Nucleo-protein	10%
		100 Tablets
Parathyroid	Nucleo-protein	5%
		20 Tablets
Pituitary	Nucleo-protein	10%
		20 Tablets
Suprarenal	Nucleo-protein	10%
		100 Tablets
Thyroid	Nucleo-protein	1%
		100 Tablets
Thyroid	Nucleo-protein	5%
		100 Tablets
Thyroid	Nucleo-protein	10%
		100 Tablets

SPECIAL FORMULAE

Each formula is sold in bottles of 40 and 100 capsules or tablets.

No. 1 Glandular Comp. Male Hypoadrenia, Asthenia, Low Blood Pressure, Fatigue Syndrome	Thyroid Pituitary Suprarenal Orchic Physiological Salts Comp.	grs. 1/10 " 1/40 " ¼ " ¼ " ¼	Dose: 1 or 2 tablets or capsules 3 times daily.
No. 2 Glandular Comp. Female Hypoadrenia, Asthenia, Low Blood Pressure, Fatigue Syndrome	Thyroid Pituitary Suprarenal Ovarian Physiological Salts Comp.	grs. 1/10 " 1/40 " ¼ " ¼ " ¼	Dose: 1 or 2 tablets or capsules 3 times daily.
No. 3 Pineal Comp. Male Backward Children, Mongolism, Retarded Mental or Physical Development	Anterior Pituitary Thyroid Suprarenal Orchic Pineal Physiological Salts Comp.	grs. 1/5 " ⅛ " 1 " 1½ " 1/30 " ¼	Dose: 1 or 2 tablets or capsules 3 times daily.
No. 4 Pineal Comp. Female Backward Children, Mongolism, Retarded Mental or Physical Development	Anterior Pituitary Thyroid Suprarenal Ovarian Pineal Physiological Salts Comp.	grs. 1/5 " ⅛ " 1 " 1½ " 1/30 " ¼	Dose: 1 or 2 tablets or capsules 3 times daily.
No. 5 Orchic-Prostate Comp. Enlarged Prostate, Sexual Neurasthenia, Vesical Irritation	Orchic Prostate Calcium Glycerophosphate	grs. 1 " 2 " 2	Dose: 2 or 3 tablets or capsules 3 times daily.
No. 6 Corpus Luteum Comp. Vomiting of Pregnancy (Hyperemesis Gravidarum), Menstruation Psychosis, Mild Manic Depressive Insanity (Females)	Corpus Luteum Thyroid Physiological Salts Comp.	grs. 1 " 1/10 " ¼	Dose: 1 to 3 tablets or capsules every 3 or 4 hours, which may be increased to 5 tablets in unusually severe cases.
No. 7 Parathyroid Comp. Tetany, Uremia, Epilepsy, Paralysis Agitans, Nervous Tremor of Children	Parathyroid Orchic Calcium Lactate	grs. 1/20 " 1 " 2	Dose: 2 or 3 tablets or capsules 3 times daily.
No. 8 Thymus Comp. Chronic Arthritis, Rheumatoid Arthritis, Arthritis Deformans	Thymus Thyroid Pituitary	grs. 3 " 1/10 " 1/20	Dose: 1 or 2 tablets or capsules 3 times daily.
No. 9 Mammary Comp. Menorrhagia, Metrorrhagia, Subinvolution, Prolonged Menses, Uterine Oozing	Mammary Posterior Pituitary Calcium Lactate	grs. 2 " ½ " 2	Dose: 1 or 2 tablets or capsules 3 times daily.
No. 10 Suprarenal-Pituitary Comp. Asthma, Bronchial Asthma	Suprarenal Pituitary Entire Thyroid Anterior Pituitary Physiological Salts Comp.	grs. 2 " ½ " 1/10 " 1½ " ¼	Dose: 1 or 2 tablets or capsules 3 times daily, which may be increased when asthmatic aura appears.
No. 11 Ovarian Comp. Amenorrhea, Ovarian Hypofunction, Menopause	Ovarian Substance Thyroid Physiological Salts Comp.	grs. 3 " 1/10 " ¼	Dose: 1 or 2 tablets or capsules 3 times daily, which may be increased to 3 or 4 tablets from 5 to 10 days before the expected menstrual period.
No. 12 Renal-Pancreas Comp. Nephritis, Prevention of Uremia	Kidney Substance Pancreas Sub. Physiological Salts Comp.	grs. 2 " 2 " ¼	Dose: 1 or 2 tablets or capsules 3 times daily.